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ASH Co-Sponsors Inaugural National Conference on Blood Disorders in Public Health and Promotes the Important Role of Hematologists

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This past March, ASH, along with the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), and the National Heart, Lung, and Blood Institute (NHLBI), co-sponsored the first National Conference on Blood Disorders and Public Health. The purpose of this conference was to begin to develop a nationally recognized public health framework for promoting the health of and improving outcomes among people at risk for or affected by non-malignant blood disorders. Public health interventions focus on preventing rather than treating a disease through surveillance of cases and the promotion of healthy behaviors. In helping to design the conference, ASH tried to incorporate the critical role of a hematologist in implementing effective public health strategies to prevent hematologic disease.

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DIFFUSION

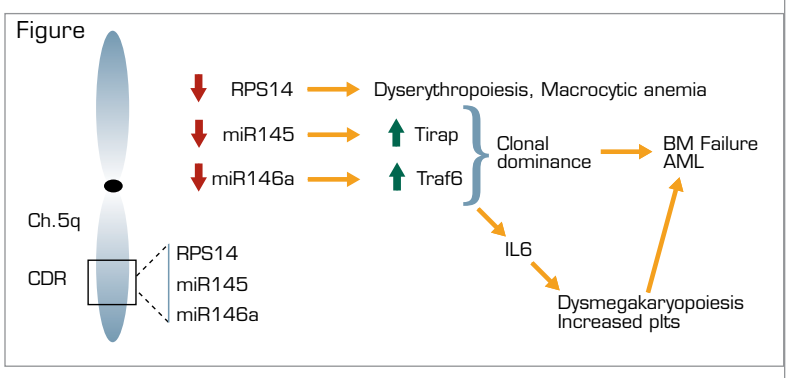
Clarifying the Genetic Underpinnings of the 5q- Syndrome

Starczynowski DT, Kuchenbauer F, Argiropoulos B, et al. Identification of miR145 and miR146a as mediators of the 5q- syndrome phenotype. Nat Med. 2010;16:49-58.

Myelodysplastic syndromes (MDS) comprise a group of clonal hematopoietic diseases characterized by cytopenias, dysplasia in one or more of the major myeloid lineages, ineffective hematopoiesis, and an increased risk of development of acute myeloid leukemia (AML). In some cases of MDS, all or part of one copy of the long arm of chromosome 5 (5q) is deleted in cells of the myelodysplastic clone. The degree of deletion within 5q can vary, and molecular studies have revealed a commonly deleted region (CDR) that is required for the 5q- syndrome, the specific findings of which include refractory anemia and normal or elevated platelet counts with dysplastic micromegakaryocytes in the bone marrow (BM). The CDR is about 1.5 million bases long and encodes many different genes. In 2008, Ebert and colleagues, then in the laboratory of Todd Golub, showed that haploinsufficiency of the RPS14 gene, which is within the CDR, alone was able to cause refractory anemia analogous to that found in the 5q- syndrome.[1] In this recent manuscript from the laboratory of Aly Karsan in Vancouver, Starczynowski and colleagues show that deletion of two microRNAs, miR145 and miR146a, which also lie within the CDR, can cause megakaryocytic dysplasia with increased platelets and can lead to BM failure and AML. MicroRNAs (miRs) are small, 18- to 24-nucleotide non-coding RNAs that regulate either stability or translation into protein of partially complementary target messenger RNA molecules.

The investigators first showed that the expression levels of miR145 and miR146a are decreased in the MDS cells from patients with 5q- syndrome, whereas they are expressed normally in MDS cells with intact 5q from other patients. When the investigators knocked down expression of miR145 and miR146a in mouse BM, the mice developed many aspects of the 5q- syndrome, including dysplastic megakaryocytes and elevated platelet counts, but erythropoiesis was normal in these mice. Over time, loss of miR145 and miR146a led to loss of normal hematopoietic cells in the BM, a phenomenon referred to as clonal dominance, which led to either BM failure or AML in the mice.

Based on their RNA sequence, miR145 and miR146a potentially target more than 500 genes, and miR146a has been implicated in many diseases including ALL, AML, rheumatoid arthritis, and breast cancer.[2] In order to determine the mechanism(s) by which loss of miR145 and miR146a cause the 5q- syndrome, the investigators studied two target genes of these miRs, TRAF6 and TIRAP, that have been implicated in the innate immune system. When the investigators overexpressed TRAF6 (which is not only down-regulated by miR146a, but also activated by TIRAP, which in turn is down-regulated by miR145) in mouse BM, they again produced a phenotype similar to the 5q- syndrome with evolution to either AML or BM failure. Because interleukin 6 (IL6) is known to be up-regulated by TRAF6, they tested the effects of TRAF6 overexpression in IL6 knockout mice. Although the mice did not develop abnormal megakaryocytes, they did develop AML. Thus, IL6 appears to mediate TRAF6's effect on megakaryocytes and platelets, whereas TRAF6 alone eventually causes clonal dominance and progression to leukemia.



Whether the puzzle of the 5q- syndrome is solved remains to be shown; these studies beautifully complement those showing that haploinsufficiency of RPS14 causes the erythroid dysplasia in MDS and suggest that haploinsufficiency of RPS14 plus miR145 and miR146a may cause all of the known manifestations of the 5q- syndrome.

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2. Li L, Chen XP, Li YJ. MicroRNA-146a and human disease. Scand J Immunol. 2010;71:227-231.

DIANE KRAUSE, MD, PhD

Dr. Krause indicated no relevant conflicts of interest.

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COVER STORY

ASH Co-Sponsors Inaugural Conference

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During the conference, there were simultaneous sessions that presented innovative public health strategies to prevent or reduce the burden of blood disorders. In addition, the conference showcased evidence-based public health strategies designed to prevent and/or eliminate blood disorder-related health disparities.

Approximately 400 individuals attended the conference, including representatives from state and federal agencies, patient advocacy groups, public health practitioners, and medical professionals. The breadth and depth of expertise was refreshing, and the extensive networking opportunities were quite impressive. Despite their common interests, individuals from the various disciplines of hematology, health policy, health services research, and public health rarely have the opportunity to attend the same meetings and discuss their specific viewpoints regarding blood disorders.

State Health Officer Maxine Hayes, MD, MPH, from the Washington State Department of Health delivered the keynote address. Her poignant presentation titled "Non-Malignant Blood Disorders: Is There a Role for Public Health?" focused on how common blood diseases such as hemophilia, venous thromboembolism, and sickle cell disease are, but how infrequently they are considered public health diseases. In fact, Dr. Hayes pointed out that each disease meets the major criteria required to be considered a public health disorder.

Other highlights of the meeting included sessions on the public health response to blood disorders. Public health leaders and hematologists Drs. Susan Shurin from NHLBI, Michael Soucie from the CDC, and Gary Raskob from the Oklahoma School of Public Health delivered presentations on sickle cell disease, thalassemia, hemophilia, deep-vein thrombosis, and pulmonary embolism. The sessions provided a solid foundation for developing partnerships between various federal agencies that have distinct programs for each of the blood disorders. After each session, the speakers were peppered with lively questions from the audience, including specific challenges regarding the lack of a common agenda between the federal agencies, public health departments, academics, and advocacy groups. The conference really energized attendees to look at blood disorders from a broad perspective and to begin to discuss the need to create a unified public health response to the needs of people with blood disorders.

ASH members were well represented at the conference and are encouraged to participate in the ongoing dialogue about creating public health strategies to prevent blood disorders. By working together with our public health colleagues, hematologists can incorporate blood diseases in federal and state public health priorities so that, working together with practitioners, we can decrease the burden of blood disorders. This nascent movement will undoubtedly gain momentum; all interested ASH members are encouraged to stay tuned for future opportunities.

The Society's participation in the conference is part of a broader ASH initiative to create a public health response for blood disorders. ASH recently developed a work group to help guide the Society's public health agenda; anyone interested in participating in this effort should contact ASH Government Relations Manager Stephanie Kart at skart@hematology.org or 202-776-0544.

LETTERS TO THE EDITOR SOLICITATION

The Hematologist welcomes letters of up to 200 words. These letters may be in response to editorials or on any subject of interest to our readers. Please include a postal address, e-mail address, and phone number. Publication will be based on editorial decisions regarding interest to readers and space availability. We may edit letters for reasons of space or clarity. *The Hematologist* reserves the right to publish your letter, unless it is labeled "not for publication."

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President's Column

Reaching Out

In its continuing efforts to understand and utilize state-of-the-art information in hematology for clinical benefit and to educate its members and the public, ASH has reached out to, and interacted with, other clinical and scientific societies within and outside the United States. I have the pleasure of briefly updating you on two recent meetings ASH was involved in.

On May 10, ASH held a guest symposium at the 97th Annual Meeting of the American Association of Immunologists (AAI) in Baltimore, MD. The concept was for AAI and ASH members to get to know each other better, since both societies involve the study of blood and immune cells, and to inform AAI members about our Society. The symposium was titled "Stem Cell Biology, the Niche, and Hematopoietic Cell Engraftment," and I co-chaired it along with Dr. David Scadden, Massachusetts General Hospital and the Harvard Stem Cell Institute. Dr. Irving L. Weissman, Stanford University, covered "Stem Cell Biology and Characterization," Dr. Hiromitsu Nakauchi, University of Tokyo, discussed "The Hematopoietic Stem Cell Signature," Dr. David Scadden elucidated "The Hematopoietic Stem Cell Niche," Dr. George Q. Daley, Children's Hospital Boston and the Harvard Stem Cell Institute, talked about "Embryonic Stem Cells, Induced Pluripotent Stem Cells, and Reprogramming," and I covered "Enhancing Engraftment and Recovery of Hematopoietic Stem Cells." Active discussion in response to audience questions occurred after all the talks were finished. We are indebted to the speakers, many of whom had to reorganize their schedules to speak at this symposium. Special thanks to Ulyana V. Desiderio, Scientific Affairs Manager, who helped make this symposium a reality.

The second Highlights of ASH® Latin American (HOA-LA) took place in Rio de Janeiro, Brazil, May 14-15. Success was highlighted even before the meeting took place. Registration was closed one month early after more than 500 individuals registered for the meeting. The program was co-chaired by Drs. Armand Keating, vice-president of ASH, Princess Margaret Hospital, Toronto; Alexis Thompson, Northwestern University, Chicago; Richard Van Etten, Tufts University Medical Center, Boston; José Orlando Bordin, Associação Brasileira de Hematologia e Hemoterapia; and Carlos Chiattone, from the same Society. The program featured 19 speakers, eight panel discussions, and a breakfast with speakers as table hosts. Panel discussions were facilitated by moderators from Uruguay, Paraguay, Bolivia, Chile, Argentina, Peru, and Brazil. Success was ensured by the efforts of speakers and organizers from ASH and Associação Brasileira de Hematologia e Hemoterapia, the National Hematology Society in Brazil, and through generous contributions of the Wallace H. Coulter Foundation, which provided support that makes international programming possible. This support funded travel awards for 25 trainees from seven Latin American countries. We acknowledge the vision, encouragement, and support of the HOA-LA from the Wallace Coulter Foundation.

In June, we had the joint ASH/American Society of Clinical Oncology (ASCO) symposium at the annual ASCO meeting in Chicago, and the joint ASH/European Hematology Association (EHA) symposium at the annual EHA meeting in Barcelona, Spain. We look forward to updating you on these events in the future.

Hal E. Broxmeyer, PhD

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2010 ASH® State-of-the-Art Symposium
Advances in Hematologic Malignancies and Thrombotic Disorders

Palmer House Hilton
Chicago, IL
September 24-25, 2010

This year's program will be presented by hematology experts who will discuss new advances in the treatment, diagnosis, and management of hematologic malignancies and thrombotic disorders. This clinically focused CME program was designed as a supplement to the ASH annual meeting and offers the same exceptional educational content to hematologists, hematologist-oncologists, oncologists, trainees, allied health professionals, and hematopathologists. The small-meeting setting allows ample time for one-on-one and small-group discussions with speakers and colleagues. Join us at the 2010 State-of-the-Art Symposium to share and learn new practice strategies for managing your day-to-day patient cases. For more information about this meeting, including program schedule and registration information, go to *www.hematology.org/SAS.*

ASH Members Elected to the National Academy of Sciences

Vann Bennett, MD, PhD
Investigator, Howard Hughes Medical Institute; James B. Duke Professor of Cell Biology, Departments of Cell Biology, Biochemistry, and Neurobiology, Duke University Medical Center

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Investigator, Howard Hughes Medical Institute; Chairman, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center

ASH Members Named Fellows of the American Academy of Arts and Sciences

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Editor Search Announcement

ASH is looking for the next Editor-in-Chief of *The Hematologist* (term: 2012-2014). Candidates with an MD or equivalent medical degree should have a broad and comprehensive knowledge of basic research and clinical investigation in hematology as well as an appreciation of its subspecialty areas, a distinguished research and publications record, high standing among peers, and demonstrated writing, reviewing, and editing skills.

Members of ASH are invited to submit the names of potential candidates, accompanied by a brief, informal endorsement and a brief description of the candidate's editorial experience.

Self-nominations are being accepted as well; include a CV and a brief description of your editorial experience and why you would be a good editor, and send it to:

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The application deadline is September 1, 2010.

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Ask the Hematologist

MICHAEL H. KROLL, MD

Professor or Medicine and Chief of the Section of Benign Hematology, Division of Internal Medicine, The University of Texas M. D. Anderson Cancer Center

(Editor's Note: The original question was submitted to Dr. Kroll through Consult a Colleague. He expanded his answer for print.)

The Question

A 78-year-old male with a bladder tumor had severe hematuria and a hemoglobin level of 8 with associated dyspnea. Urologists were unable to evaluate secondary to severe bleeding in the bladder. Coagulation testing revealed a normal prothrombin time (PT) of 10 seconds, but his activated partial thromboplastin time (aPTT) was elevated at 108 seconds, lowering to 56 seconds when mixed with normal plasma. Levels of coagulation factors VIII, IX, X, XI, and XII were normal, although the report noted the possibility of an inhibitor. Von Willebrand factor (VWF) studies were normal, as were assays for anticardiolipin antibodies (ACA) and lupus anticoagulant (LA). The patient continues to bleed and his hemoglobin continues to drop. Should any other work-up be done? Given that he had no benefit from fresh frozen plasma infusions, should I give factor VII complex?

My Response

Bleeding is impaired hemostasis and therefore can be evaluated from the same perspective that Virchow organized for thrombosis — as dysfunction within the triad of blood (mainly soluble coagulation factors, fibrinolytic apparatus, or platelets), blood vessel (mainly its structural integrity or permeability), and/or blood flow (mainly the effects of ischemia or hyperperfusion). In most cases of bleeding, a simple, single explanation emerges. But in more complicated cases, like the one in question, I try to identify and rank the hemostatic elements that have broken down.

When I see bleeding from the bladder, I focus first on tumor-associated hemorrhage. This is because one must immediately direct therapy toward the cancer, if the fundamental pathophysiological element is tumor-erosive hemorrhage. But how does one establish the diagnosis if hematuria is so severe as to prevent visualization and biopsy of the bladder mucosa? I would retreat slightly and look for disturbed and perhaps related hemostatic elements that could be reversed and thereby permit proper evaluation of the root cause of the hematuria.

When there is severe hematuria, perhaps related to transitional cell carcinoma, I ask the question: Is there hyperfibrinolysis? The malignant urothelium is rich in urokinase-type plasminogen activator,[1] and local and sometimes systemic hyperfibrinolysis develops and contributes to bleeding in patients with bladder cancer. Systemic hyperfibrinolysis is not apparent by examining the PT and aPTT, but always results in elevated fibrin split products and d-dimers. It can be identified by thromboelastography (TEG) or by measuring the euglobulin lysis time. Neither test is available in every clinical laboratory, but in our institution we perform TEG. When there is hyperfibrinolysis, or anything else that de-stabilizes polymerized fibrin, the TEG tracing over 30 to 60 minutes shows a decline in the clot tensile strength — the plateau begins to decay or decline.[2] When hyperfibrinolysis is identified, one can try to control it with an antifibrinolytic drug such as aminocaproic acid or tranexamic acid.[3] The main risk of these treatments in someone with hematuria is ureteral obstruction if blood refluxes and clots in a ureter, so one must monitor urine output and serum creatinine concentration closely.

In this patient, there may be a weak coagulation factor VIII inhibitor. The isolated elevated aPTT must reflect a deficiency of, or an inhibitor to, either factor XII, XI, IX, or VIII and the incomplete aPTT correction with mixing (from 108 to 56 seconds) indicates that there is an inhibitor. The most commonly seen inhibitor is a lupus anticoagulant, which is an antiphospholipid antibody that prolongs an *in vitro* clotting assay, which, in this case, would be the aPTT. But lupus anticoagulants are not associated with bleeding — except in the rare case where they have antiprothrombin activity[4] — and this patient's anticardiolipin antibody assay and lupus anticoagulant screen were normal. So the most parsimonious explanation for this case of bleeding and abnormal coagulation studies is the presence of the most common acquired inhibitor encountered in a bleeding patient: an acquired factor VIII inhibitor. It can emerge in patients with solid tumors,[5] including bladder cancer.[6] It almost always causes clinically significant bleeding that can be controlled with a pharmacological intervention such as recombinant activated factor VII (rFVIIa).[7] And the inhibitor itself (an auto-antibody to factor VIII that causes rapid clearance) is often reduced or eradicated with immunosuppressive therapy.[8] To evaluate for this possibility, I suggest repeating the factor VIII assay and measuring the inhibitor titer in Bethesda units, which is the inverse of the dilution of the patient's plasma that decreases factor VIII activity in control plasma by 50 percent. My speculation is that when this patient's factor VIII level is repeated, it will be borderline low or low and that he will have an inhibitor level < 5 units. If an inhibitor is identified, I would administer rFVIIa, although some would first try human factor VIII in cases of low titer acquired factor VIII inhibitors.[8]

Should one use rFVIIa under any circumstances? Assuming that the PT and platelet count remain satisfactory, I would first try bladder irrigation. If this or other urological manuevers don't work and everyone remains mystified by the pathophysiology, I would begin aminocaproic acid at an infusion rate of 1 gm/h. If aminocaproic acid doesn't work, I would then add rFVIIa, but only at 20 to 30 mcg/kg and beginning at four- or even six-hour intervals.[9] This dose is prohemostatic but probably causes fewer thromboses than the conventional dose of 90 mcg/kg every two hours.[10]

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Dr. Kroll is part of Eisai's Speakers' Bureau.

Need to Consult a Colleague?

Through the Consult-a-Colleague program, ASH members can seek consultation on clinical cases related to:

- **Hemostasis/thrombosis**
- **Lymphoproliferative disorders**
- **Myeloproliferative disorders**
- **Myelodysplastic syndromes**
- **Multiple myeloma/Waldenström macroglobulinemia**

To submit a question, go to *www.hematology.org/Practice/Consult-a-Colleague.* You will receive a response to your inquiry within two business days.

JAK Inhibitors in Myeloproliferative Neoplasms

AYALEW TEFFERI, MD

Professor of Medicine and Hematology, Division of Hematology, Mayo Clinic College of Medicine

Next year will mark the golden anniversary of the first formal description of the classic myeloproliferative neoplasms (MPNs): polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myelogenous leukemia (CML).[1] We now recognize these MPNs as stem cell-derived clonal (or oligoclonal) disorders that display mature-appearing but abnormally increased myeloproliferation. The disease-causing mutation in CML is *BCR-ABL1*, and kinase inhibitors (e.g., imatinib, dasatinib) that target its corresponding oncoprotein have been shown to be therapeutically effective.[2] In contrast, the genetic underpinnings of PV, ET, and PMF remain poorly understood and their treatment suboptimal.

Beginning in 2005, novel mutations involving *JAK2, MPL, TET2, ASXL1, IDH1, IDH2, CBL, IKZF1,* or *LNK* have been described in a subset of patients with *BCR-ABL1*-negative MPN.[3] However, none of these mutations garner the disease specificity or pathogenetic relevance otherwise displayed by *BCR-ABL1.* Furthermore, with the exception of *JAK2*V*617F,* which occurs in approximately 95 percent of patients with PV and 60 percent of those with ET or PMF, the mutational frequencies of these individual genes seldom exceeds 10 percent. Nonetheless, considering the fact that some of these mutations either directly (e.g., *JAK2* or *MPL* mutations) or indirectly (e.g., *LNK* or *CBL* mutations) induce JAK-STAT hyperactivation, a number of ATP mimetic kinase inhibitors with activity against JAK2 have been developed and are currently undergoing clinical trials (see Table for summary).

Phase I/II studies of CYT387[4] and AZD1480[5] in MPN were initiated only a few months ago, and study results are too preliminary to warrant any comments at this point. Clinical trials with XL019 are currently on hold because of concerns regarding neurologic toxicity, but the drug did show activity against splenomegaly and leukocytosis in PMF or post-PV/ET MF patients with *JAK2* or *MPL* mutatations.[6] Preliminary results with SB1518 in patients with myelofibrosis suggest activity against splenomegaly; nausea and diarrhea were the main side effects.[7] CEP-701 is also associated with gastrointestinal side effects, and its therapeutic activity, so far evaluated in *JAK2*V*617F*-positive patients only, has been underwhelming; in MF, four of 22 patients experienced spleen size reduction and two became red cell transfusion-independent, whereas the drug was unexpectedly associated with thrombotic complications in PV/ET.[8,9]

Fifty-nine patients with PMF or post-PV/ET MF have been treated with TG101348.[10] The majority of evaluable patients achieved a > 50 percent reduction in palpable spleen size and resolution of leukocytosis, thrombocytosis, and constitutional symptoms including pruritus. In addition, a > 50 percent reduction in JAK2V617F allele burden was documented in 44 percent of evaluable cases. Side effects included gastrointestinal symptoms, anemia, thrombocytopenia, and dose-dependent and reversible increase in serum transaminase, amylase, or lipase levels. INCB018424 has been evaluated in 155 MF and 73 PV/ET patients.[11,12] At the optimal dose level, 48 percent of evaluable PMF patients achieved > 50 percent reduction in spleen size, and complete hematologic remission rates in both PV and ET were < 50 percent. The drug was most effective in alleviating constitutional symptoms, including pruritus and cachexia, and this activity correlated with marked reduction in serum pro-inflammatory cytokines. Of note, serum cytokine levels did not appear to be affected by TG101348 or CEP-701.[8] Side effects of INCB018424 included thrombocytopenia, anemia, and, in some patients, acute and immediate (i.e., within days) reappearance of symptoms upon drug discontinuation, which is believed to be related to a cytokine rebound effect. The drug had little effect on JAK2V617F allele burden.

Taken together, it is reasonable to make the following conclusions:

- JAK2 inhibitors currently undergoing clinical trials show substantial inter-drug differences in their toxicity and efficacy profiles. Some of these differences might be linked to their variable activity against other JAK and non-JAK kinase targets. Therefore, at this point in time, it is both premature and inappropriate to make general statements regarding the prospect of anti-JAK2 therapy in MPN. In other words, many more such drugs should be evaluated in order to appreciate the full spectrum of their benefit.
- Off-target activity of specific JAK2 inhibitors appears to matter. The accompanying figure illustrates the spectrum of cytokines that are differentially affected by inhibition of a specific JAK protein. Currently available information supports the assumption that both improvement in constitutional symptoms and "cytokine rebound phenomenon" from INCB018424 are related to its anti-JAK1 activity and mediated by drug-induced alteration in proinflammatory cytokines. Similarly, off-target FLT3 inhibition displayed by TG101348, CEP-701, and SB1518 might contribute to their common side effect profile of nausea, vomiting, and diarrhea.
- On-target anti-JAK2 activity contributes to drug-induced anemia and thrombocytopenia seen with JAK2 inhibitor therapy. These drug effects are dose-dependent and might come in handy in the treatment of PV or ET. More selective anti-JAK2 drugs, such as TG101348, might be preferable in the setting of PV or ET because of their superior activity in controlling leukocytosis, thrombocytosis, and JAK2V617F allele burden as well as avoidance of extraneous and potentially harmful anti-JAK1 drug activity.

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(Cont. on Page 6)

Figure

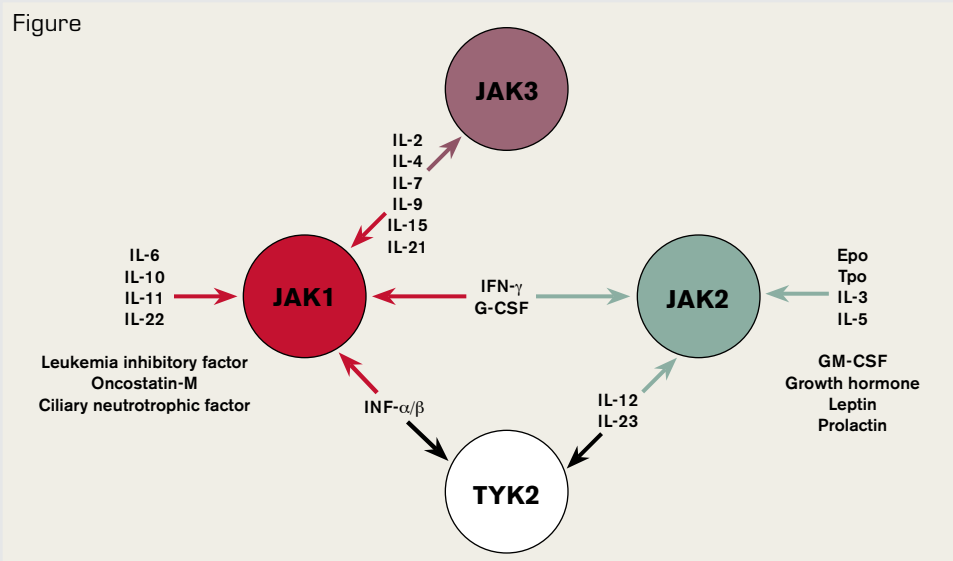

Table: List of JAK2 Inhibitors Currently Undergoing Clinical Trials

IC50 = concentration producing 50 percent inhibition; UNK = unknown; DLT = dose-limiting toxicity

Anti-JAK2 drug	Anti-JAK2 IC50 (JAK1/JAK3/TYK2 selectivity)	Non-JAK kinase targets	Clinical trials	Disease features shown to be favorably affected	Side effects
INCB018424[11,12] (Phase I/II study)	4.5 nM (x0.6/x72/x4)		MF (*n*=155) PV (*n*=34) ET (*n*=39)	Splenomegaly Constitutional symptoms Pruritus Cachexia Erythrocytosis (PV)	Thrombocytopenia (DLT) Anemia Cytokine rebound phenomenon*
TG101348[10] (Phase I/II study)	3 nM (x35/x332/x135)	FLT3 RET	MF (*n*=59)	Splenomegaly Constitutional symptoms Pruritus Leukocytosis Thrombocytosis *JAK2*V617F burden	Anemia Thrombocytopenia Nausea/vomiting Diarrhea Increased transaminases Increased amylase/lipase (DLT)
CEP-701[8,9] (Lestaurtinib) (Phase II study)	1 nM (UNK/x3/UNK)	FLT3 TrkA	MF (*n*=22) PV (*n*=27) ET (*n*=12)	Splenomegaly Anemia (MF) Pruritus	Diarrhea Nausea/vomiting Anemia (MF) Thrombocytopenia (MF) Thrombosis (PV/ET) Leukocytosis (PV/ET) Thrombocytosis (PV/ET)
CYT387[4] (Phase I/II study)	18 nM (x0.6/x8.6/UNK)	JNK1 CDK2	MF	Results pending	Results pending
AZD1480[5] (Phase I/II study)	0.26 nM (x5/x15/UNK)	TrkA Aurora A FGFR1	MF	Results pending	Results pending
SB1518[7] (Phase I/II study)	22 nM (x58/x24/UNK)	FLT3	MF (*n*=31)	Splenomegaly	Diarrhea Nausea Thrombocytopenia (DLT=GI symptoms)
XL019[6] (Phase I/II study)	2 nM (x67/x98/x172)		MF (*n*=21)	Splenomegaly Constitutional symptoms Leukocytosis	Neuropathy (DLT) No myelosuppression

*Consists of acute and immediate (i.e., within days) reappearance of symptoms and enlargement of spleen that has required hospitalization for some patients.

HEADLINES FROM Washington

ASH Seeks to Increase Funding for NIH in FY 2011

As this issue went to press, the House and Senate had yet to finalize a fiscal year (FY) 2011 Budget Resolution, the budgetary blueprint for each Appropriations subcommittee to use as a guideline in drafting their respective funding bills. Congressional leaders remained hopeful, however, that budgetary guidelines would be in place by early summer in order to allow House and Senate appropriators to begin formal work on all 12 of the annual spending bills.

ASH, along with the biomedical research community, continues to advocate for $35 billion for NIH in FY 2011 to help ensure that NIH does not face a funding crisis when a two-year allotment of $10.4 billion in stimulus funding for research expires. ASH encourages all members to visit the ASH Advocacy Center (*www.hematology.org/takeaction*) to take action to help influence the budget process and support increased funding for NIH. Your senators and representatives need to hear from you about ensuring adequate NIH funding in FY 2011.

Dr. Donald Berwick Nominated for CMS Administrator

President Barack Obama has nominated Dr. Donald M. Berwick to lead the Centers for Medicare and Medicaid Services (CMS), the federal agency that administers Medicare, Medicaid, and the Children's Health Insurance Program, and the federal agency responsible for implementing many new programs enacted in health reform. Dr. Berwick, who is currently the CEO of the Boston-based Institute for Healthcare Improvement and a Pediatrics and Health Policy professor at Harvard University, has devoted his career to examining methods of delivering care more safely and efficiently to saves lives and reduce wasteful spending.

Dr. Berwick could face tough confirmation hearings, which are expected to begin in July. Although he has extensive leadership and health policy experience, he has no previous government executive experience. In addition, Republican senators might seek a hold on his nomination or use his confirmation hearings to show their lingering displeasure with the health-care overhaul.

Nobel Laureate Harold Varmus to Head NCI

President Barack Obama has named Dr. Harold Varmus, who shared the 1989 Nobel Prize for physiology or medicine, to head the National Cancer Institute (NCI) at NIH. Dr. Varmus, who is currently president of Memorial Sloan-Kettering Cancer Center in New York, shared his Nobel Prize with J. Michael Bishop for demonstrating the cellular origins of the oncogene of a chicken retrovirus, which led to the isolation of many cellular genes that normally control growth and development and are frequently mutated in human cancer.

Dr. Varmus will become the first former NIH director — a position he held under President Bill Clinton from 1993 to 1999 — and Nobel laureate to lead NCI. Dr. Varmus' appointment does not require Senate confirmation; he is expected to start at NCI in mid-July.

NIH Proposes Revisions to Financial Conflict-of-Interest Regulations

On May 20, NIH unveiled a Notice of Proposed Rulemaking (NPRM) seeking to amend current regulations governing the disclosure, reporting, and management of financial conflicts of interest. NIH proposes to make several revisions to the rules governing financial disclosure that have been in place since 1995, including:

- Lowering the threshold for determining if a "significant financial interest" exists to $5,000.
- Requiring investigators to disclose to their institutions all "significant financial interests" related to their institutional responsibilities and research.
- Requiring institutions to review the "significant financial interests" disclosed by investigators to determine those that may or may not impact NIH-funded research and to post these financial interests on a publicly accessible website.

NIH will be soliciting public comments and input through July 20. ASH will be reviewing this issue in detail and submitting comments in response to the NPRM. All ASH members are encouraged to submit any particular concerns or comments on this issue to ASH Research Advocacy Manager Tracy Roades at *troades@hematology.org*.

Congress Struggles to Address Medicare Physician Payment

As this issue went to press, Congress was still seeking agreement on a long-term solution to address impending Medicare physician payment cuts, and physicians were scheduled to receive a 21 percent payment cut until legislation restoring the cut could be enacted.

Despite reaching agreement in mid-May on a proposal that would have provided a four-year physician payment fix, House lawmakers scaled down a physician payment adjustment proposal to respond to concerns about the cost of the overall legislation. Under the compromise, physicians would receive a 2.2 percent increase effective June 2010 and a one percent increase on January 1, 2011. Physician payment rates would revert to the current law formula on January 1, 2012, which will result in an estimated 33 percent payment cut that year. However, it was still not confirmed that Senate lawmakers would agree to the compromise.

Citing insufficient time to consider the legislation before the congressional Memorial Day recess, the Senate adjourned until June 7 and the 21 percent Medicare physician payment cut scheduled for 2010, which had been postponed three times already this year, technically took effect on June 1. The Centers for Medicare & Medicaid Services, however, issued instructions to its contractors to postpone processing claims for Medicare physician services provided on or after June 1 for 10 days to provide time for Congress to complete its action and overturn the scheduled cut retroactive to June 1.

Updated information about this issue is available on the ASH website at *www.hematology.org*. Physicians are encouraged to visit the ASH Advocacy Center (*www.hematology.org/takeaction*) to contact their representatives and senators to urge a permanent fix of the physician payment formula.

Mini Review

(Cont. from page 5)

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Perspectives on the Hematology In-Service Examination

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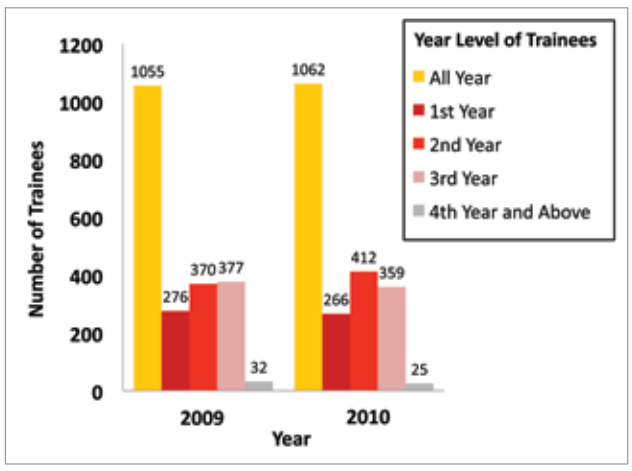
Chair, ASH Trainee Council

This is the second year of the hematology in-service examination. Clinical hematology fellows at various levels of training from all over the country and several participants from Canadian programs took the six-hour and 15-minute examination in April 2010 (Figure). An endeavor of the American Society of Hematology (ASH), the examination provides an objective assessment instrument for the medical knowledge competency of the Accreditation Council for Graduate Medical Education (ACGME)/ Residency Review Committee (RRC).

Chair of ASH's Committee on Training Programs Dr. Scott Gitlin explained that the exam was designed to help both program directors and trainees in a variety of ways. For program directors, the examination provides an objective assessment of the level of medical knowledge in hematology of their individual trainees and serves as a benchmark and tool to improve training by identifying areas of strengths and weaknesses in their programs. For fellows, it allows for the evaluation of progress both within their training program and in comparison to national outcomes.

I had the opportunity to speak with a couple of trainees and program directors regarding the exam. Dr. Ryan Mattison, an assistant professor in the School of Medicine and Public Health at the University of Wisconsin, who took his examination in 2009, said, "It was a fair exam. It was well balanced in what you are supposed to learn in hematology. When I received my feedback, I was able to recognize areas in hematology in which I was deficient, which allowed me to focus my reading on the American Board of Internal Medicine certification exam." Dr. Julie Nangia, a third-year hematology and oncology fellow at Rush University Medical Center, took the exam in both 2009 and 2010. She was equally satisfied with each setting, and said, "I think that the exams were fair with a good representation of leukemia/lymphoma and benign hematology topics. I received my feedback in a timely fashion



and was able to meet with my program director to discuss the results." She expressed that it would be useful if the feedback process could be patterned similar to the internal medicine residency in-service exams, in which specific answers are not given out but the specific learning points are mentioned. Such a change is being implemented for the 2010 exam; the exam scores will be accompanied by learning-objective statements for the questions that were incorrectly answered.

From the perspective of a program director, Dr. Robert Dean, of the Cleveland Clinic Foundation, is very pleased that such an exam is available. "I believe that it allows the program director to design the fellowship curriculum according to areas of strength and weakness of the fellows. It also gives some guidance on which additional rotations may be most helpful." With regard to having all fellows take the exam, he felt that it would probably be most useful for second- and third-year fellows, since their baseline knowledge is more developed. However, Dr. Jamile Shammo, from Rush University Medical Center in Chicago, said that the exam can be useful for all years of fellowship training and that it can help fill important knowledge gaps for trainees. She pointed out that "it will also allow for improving documentation of ACGME competency."

I personally experienced the ASH in-service exam on April 6, 2010. I felt that it was a useful examination for providing personal feedback to fellows and their program directors. The examination was well balanced in topics covered and provided sufficient time for completion. And, as with any exam, rigorous attention to detail and quality control will help keep the exam up to date and useful.

The in-service examination dates for 2011 are April 5 and 6. Mark your calendar!

Top Ten Things to Remember When Submitting an Abstract to the 2010 ASH Annual Meeting

CHARLES S. ABRAMS, MD

Associate Chief, Division of Hematology-Oncology, University of Pennsylvania

Secretary, ASH

For many of us, the approach of the month of August reminds us of the end of long vacations during childhood. Now that we are hematologists, the approach of this month also reminds us of the deadline for abstract submissions to the ASH annual meeting. As the Secretary of our Society, I thought that I would remind everyone about the top 10 most important things you should know about your ASH abstract submissions.

10. Jury of your peers – This year, there are 420 reviewers, including 70 coordinating reviewers, who were carefully selected because of their expertise in one of the 56 distinct scientific categories. They are divided into teams made up of six members who evaluate the abstracts in their assigned category. Every effort is made to ensure that each individual team is composed of reviewers from geographically diverse institutions. To encourage fairness, the reviewers do not see the names of the authors or their affiliations. Once the reviewers have given a priority score to all of their assigned abstracts and the scores are averaged, the reviewers have a teleconference to select the proposed oral and poster sessions, which they submit for review by the ASH Program Committee. The Program Committee also reviews the top-scoring abstracts and selects six that will be presented at the Plenary Scientific Session.

9. How many abstracts are accepted for presentation? – Although the exact numbers vary from year to year, the data from the 2009 annual meeting are representative of our recent meetings. In 2009, a total of 5,498 abstracts were submitted to ASH. Of those abstracts, 18 percent (978 abstracts) were chosen for presentation at an oral session, and another 57 percent (3,119 abstracts) were presented as a poster.

8. New science only – Information that has already been published or presented at another meeting will not be accepted. (Occasionally, there may be exceptions. Carefully read the "Eligibility" section under 2010 Call for Abstracts on the ASH website.) ASH now uses software that compares each abstract with previously published or presented abstracts.

7. Grammar and data count – Keep in mind that an abstract that is clearly written is the best way to effectively communicate what you have accomplished. An abstract that is not clear and concise may not receive a good score. If appropriate, abstracts that include actual data with statistical analysis are easier for reviewers to assess than those containing general statements such as "increased," "decreased," or "improved."

6. Figures – If you plan to include a figure, pay close attention to the file types that are acceptable. Otherwise, your figure(s) may not be viewable to the reviewers.

5. What is not acceptable? – The same study cannot be submitted as multiple abstracts. Abstracts that have been presented elsewhere are also not acceptable. Abstracts that have been deemed unethical by the review committee are also excluded from further consideration.

4. ASH member or sponsor – One of the authors must be a current member of ASH. Otherwise, you will need a sponsor who is a member. Remember to have this information ready at the time of your submission.

3. Choose your category wisely – You are responsible for choosing the scientific category that best fits your abstract. Occasionally, an abstract scores poorly because it was submitted to an inappropriate category. Abstracts will not be re-assigned to a category different from the one chosen by the corresponding author.

2. Special consideration – If you feel you have an unusual case that deserves consideration, please state it clearly. For example, if a small portion of the abstract was already published or was presented previously, explain the situation to the reviewers. It is far better to state the rationale for requesting a special consideration, rather than leaving it unaddressed.

1. Remember the deadline approaches quickly – ASH will accept abstracts from June 14 – August 12. Just like the end of those childhood summer vacations, the due date approaches quickly. If your work is ready, it will be far less stressful to submit your abstract early, rather than to wait until the last minute.

Good luck with your abstracts. I hope to see you at the annual meeting in Orlando this December.

Irradiation Plus Recruitment Blockade of Bone Marrow-Derived Cells in Glioblastoma: Killing the Lernaean Hydra

Kioi M, Vogel H, Schultz G, et al. Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice. J Clin Invest. 2010;120:694-705.

More than 100 years ago Goldmann[1] described that a tumor is surrounded by new blood vessels, feeding it like the Lernaean Hydra in Greek mythology. Subsequently, it was hypothesized that tumors made factors to promote vessel growth. This seemed reasonable as cells need oxygen and nutrients to grow, and diffusion distances from the vasculature are limiting. Similar to Hercules cutting off each of the nine heads of the Hydra to kill it, Folkman's[2] concept that blocking angiogenesis could prevent cancer growth and metastases made sense. Newly discovered growth factors, receptors, and anti-angiogenic molecules have been identified over the past 40 years, and targeting angiogenesis is now an essential therapeutic strategy in the oncologist's armamentarium. In 2009, the FDA approved bevacizumab, an anti-VEGF monoclonal antibody, for the treatment of glioblastoma multiforme (GBM); it decreased tumor size and prolonged survival, but despite treatment, tumors grew back. Just focusing on angiogenesis may not be adequate to prevent the recurrence of glioblastoma as suggested by Kioi et al from J. Martin Brown's laboratory at Stanford. These authors showed that inhibiting vasculogenesis post-irradiation may be necessary to accomplish that end.

Human GBM cells transduced with a luciferase reporter gene were placed orthotopically into the brains of nude mice that had been transplanted with GFP-labeled bone marrow cells. Whole-brain irradiation was then delivered to cause the tumors to regress, and then the tumors were allowed to regrow. Bone marrow-derived cells (BMDCs) were shown to have influxed into the tumors. These cells were not endothelial cell progenitor cells (EPCs), but were CD11b+ myelomonocytes that expressed Tie-2 but not VEGF. Irradiation decreased CD31+ endothelial cells, decreased blood flow, and increased tumor hypoxia. HIF-1 was the key factor responsible for BMDC influx, as its inhibition abrogated BMDC influx post-irradiation. Furthermore, inhibition of HIF resulted in shrinkage of the tumor with no regrowth over time, suggesting that the BMDCs were pro-angiogenic. HIF-1 activated the chemokine SDF-1, which binds to its receptor CXCR4 on BMDCs. SDF levels rose after irradiation in the tumor, and phosphorylation of CXCR4 increased, suggesting an SDF/CXCR4 interaction. AMD3100 (plerixafor), an inhibitor of SDF-1interaction with CXCR4, prevented the blood flow in irradiated tumors and prevented tumor recurrence even more significantly than VEGF blockade. Finally, the authors showed that myelomonocytic cells were critical for tumor regrowth after irradiation. In 10 of 12 human GBM tumors examined, recurrent tumors had higher levels of CD11b+ cells compared to normal brain tissues.

This study suggests that a tumor can expand its vasculature as it grows by angiogenesis involving sprouting endothelial cells from nearby vessels or by vasculogenesis, which occurs by recruiting EPCs or BMDCs. A novel strategy to inhibit vasculogenesis after local tumor irradiation may help control tumor growth. The authors suggest that this strategy may allow lower radiation doses if only the endothelial cells and not the tumor cells need to be killed. Greenfield et al.[3] commented on this paper, cautioning that resistant endothelial cells may still play a role in explaining the BMDCs seen in recurrent tumors. Furthermore, the potential targets to prevent angiogenesis and vasculogenesis are numerous. Thus, targeting blood vessels may require a Herculean effort to cut off the numerous heads of a tumor's vascular Hydra.

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Dr. Vercellotti indicated no relevant conflicts of interest.

CD20: A Moving Target?

Beers SA, French RR, Chan CHT, et al. Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. Blood. 2010. [Epub ahead of print]

Most successful treatments invite inquiry – for example, why they work and whether there are ways to improve upon them. Rituximab, in the treatment of B-cell lymphoma and autoimmunity, is no exception, and the relative therapeutic contributions of Fc receptor-γ (FcRγ)-mediated cellular cytotoxicity, complement fixation, and direct cell surface signaling remain contentious. The characterization of two different families of anti-CD20 antibody has highlighted this: type I (rituximab-like) antibodies move the antigen into lipid rafts and are effective complement activators, whereas type II (tositumomab-like) do not redistribute antigen, but instead mediate homotypic adhesion and direct cell killing.[1] A group of researchers led by Glennie and Cragg from the University of Southampton, UK, has been investigating the underlying differences between these two types using a mouse model in which B cells express the human CD20 antigen. In this model, infusion of type II antibodies produced a much longer lasting depletion of B cells than did type I antibodies. Using mice genetically deficient in complement components, they showed the effect was independent of complement, and, using Bcl-2 overexpressing cells, they showed that resistance to apoptosis had no effect either. However, in FcRγ-chain null mice, the therapeutic effect was lost for both types of antibody, as it was when Fab fragments were used, confirming the role of FcR engagement. An examination of expression on human CD20 transgenic B cells transferred into FcR null mice showed that the antigen was apparently lost from the cell surface in response to type I antibody treatment, but not after type II. Using a fluorescence quenching assay, the authors went on to show that the loss of cell surface CD20 was due to internalization within early endosomes and lysosomes. This was accompanied *in vivo* by a significant shortening of the antibody half-life for type I but not type II and a consequent reduction in phagocytosis by macrophages in immunocompetent hosts.

CD20 has previously been thought of as a highly stable cell surface molecule, based upon short-term studies of B-cell lines and small numbers of patient samples. Indeed, this was put forward as one reason for the success of anti-CD20 therapeutics – that the antigen did not modulate. There have been a few reports of apparent loss of CD20 expression in recurrent lymphoma following antibody treatment.[2] In this paper, however, further studies of both normal peripheral blood B cells and primary malignant B cells *ex vivo* showed that type I anti-CD20 antibodies produce significant modulation of the antigen after six hours, an effect which was not seen with type II reagents. Interestingly, there was significant heterogeneity between different malignancies, with the relatively rituximab-sensitive germinal center lymphomas showing very little modulation, but CLL and mantle cell lymphoma showing much more, a finding which may relate to the differential effects seen in the clinic.

Although these experiments to elucidate the mechanisms of action of anti-CD20 antibodies may seem distant from routine clinical practice, they have important messages about how we might improve the results of treatment. First, there are several type II antibodies in clinical trials already, and it may be that these will be preferable for the treatment of those malignancies that modulate CD20 rapidly. Whether they are likely to prove superior in non-modulating lymphoma types is less clear. Second, these observations may provide a rationale for the apparently greater efficacy of high-dose type I anti-CD20 in CLL, where rapid modulation may shorten the effective half-life in many cases. Finally, if we can unravel the process by which modulation is mediated on the cell surface, we may be able to devise strategies to block it, and thereby reduce resistance to therapy.

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PETER JOHNSON, MD

Dr. Johnson indicated no relevant conflicts of interest.

Platelets Fill the Gap in Young Hearts

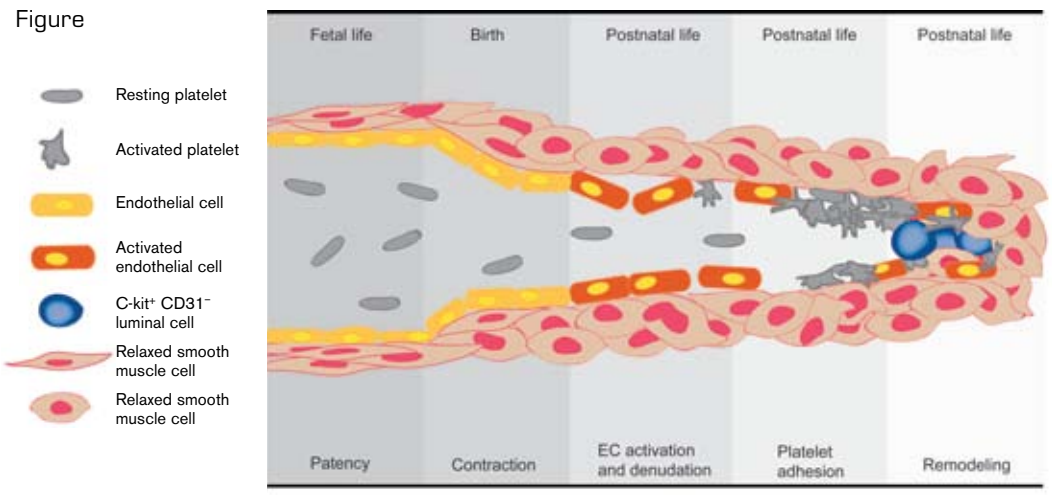
Echtler K, Stark K, Lorenz M, et al. Platelets contribute to postnatal occlusion of the ductus arteriosus. Nat Med. 2010;16:75-82.

The role of platelets in host defense is well established. They limit blood loss, stimulate inflammation, and respond to invading microbes. Platelets are also known to contribute to vascular intergrity and participate in angiogenesis and wound healing. Less well-studied is the role that platelets play in normal development. Recent studies indicate that platelets serve a role in the formation of the lymphatic system. Echtler et al. now demonstrate that platelets are crucial for permanent closure and remodeling of the ductus arteriosus following birth, providing a striking example of how platelets may contribute to normal development.

In the fetus, the ductus arteriosus shunts blood from the placenta to the aorta, bypassing the nonventilated lungs. Following birth, the ductus arteriosus closes, enabling perfusion of the newly ventilated lungs. The ductus arteriosus is subsequently remodeled into a fibrous band by mechanisms that are incompletely understood. Working in the Massberg laboratory in Munich, Echtler et al. found histological evidence of platelet accumulation within the lumen of the ductus arteriosus of newborn mice evaluated directly after birth. Intravital microscopy of newborn pups 20 minutes after birth demonstrated substantial adhesion of platelets at the ductus arteriosus, but not in the adjacent aorta. Using closure angiography, they demonstrated that mice deficient in the platelet fibrinogen receptor integrin $\alpha_{II\beta}$, mice infused with an antibody to the collagen receptor GPVI, or congenitally thrombocytopenic mice demonstrated a high incidence of persistent patency of the ductus arteriosus. The thrombocytopenic mice with persistent patency demonstrated pulmonary hypertension and right ventricular remodeling. To assess the relevance of their results to the human process, the investigators evaluated specimens from newborns undergoing cardiac surgery for congenital heart disease. They demonstrated exposure of the adhesion protein von Willebrand factor and fibrinogen as well as platelet accumulation in the lumen of the ductus arteriosus. They also performed a retrospective analysis of premature infants that demonstrated thrombocytopenia as a major risk factor for patency of the ductus arteriosus.

Persistence of a patent ductus arteriosus is a major cause of morbidity and mortality in preterm infants. The incidence is approximately 0.2 percent. However, in babies < 1,500 g, the incidence is > 30 percent. The model presented in this paper suggests that an initial contraction of the ductus arteriosus and subsequent platelet-mediated sealing are required for permanent closure. This model accounts for the observation that thrombocytopenia is associated with failed closure of patent ductus arteriosus by indomethacin, which stimulates constriction of the vessel but not sealing. These observations provide substantial evidence for platelet closure of the ductus arteriosus in mice and premature infants. The role of platelets in closure of the ductus arteriosus in mature newborns remains less clear, as hypoxia alone may stimulate sufficient remodeling. Nonetheless, these studies provide an important and unexpected role of platelets in the development of the heart.

Figure



The role of platelets for sealing of the contracted DA
The scheme delineates the proposed sequence of events contributing to postnatal DA occlusion, which ultimately leads to permanent DA closure. As a result, the luminal aspect of the DA wall adopts a prothrombotic phenotype with endothelial activation, deposition of vWF and fibrin(ogen), and eventually endothelial cell detachment from the internal elastic lamina, leading to the collagen exposure. Together, this triggers the accumulation of platelets circulating in the residual DA lumen. The platelet plug that forms seals the residual lumen of the contracted DA and, together with other mechanisms, facilitates subsequent luminal remodeling.

ROBERT FLAUMENHAFT, MD, PhD
Dr. Flaumenhaft indicated no relevant conflicts of interest.

Autophagy Promotion With Obatoclax Overcomes Steroid Resistance in Pediatric ALL

Bonapace L, Bornhauser BC, Schmitz M, et al. J Clin Invest. 2010;120:1310-1323.

Over the past three decades, considerable progress has been made in the treatment of pediatric acute lymphoblastic leukemia (ALL). Combination chemotherapy and corticosteroids administered in complicated regimens have greatly improved outcomes, with the majority of children being cured. Unfortunately, a subset of patients are either resistant to primary therapy or relapse from their disease. In each of these settings, a high proportion of corticosteroid resistance exists, which to date has been poorly characterized. The typical pathway through which most cancer therapeutics work, including those utilized in the treatment of adult ALL, is programmed cell death via caspase enzymes. In resistant ALL and other cancers, caspase activation is blocked. A recently discovered mechanism by which death can still be provoked in such cells is by induction of autophagy. Autophagy is a protective mechanism in which normal cells engulf and digest internal organelles in times of starvation or stress to promote survival. The role of autophagy in cancer, including leukemia, is somewhat variable, with some studies demonstrating a protective effect from stress, whereas others have shown it to generate a pro-death effect. Bonapace and colleagues from the lab of Jean-Pierr Bourquini in Zurich demonstrated that treatment of corticosteroid and chemotherapy-resistant ALL cells with the BCL-2 inhibitor obatoclax dramatically converted them to a very responsive state. Whereas cytotoxic therapy with obatoclax treatment promoted cell death through apoptosis, with corticosteroids the autophage pathway of autophagy was activated, leading to caspase-independent cell death. Blockade of autophagy by antagonizing expression of key autophagy-mediating genes antagonized ALL cell chemosensitization to corticosteroids, thereby demonstrating the importance of this pathway in converting cells from steroid-resistant to steroid-responsive. The molecular details underlying these phenomena were further defined by showing that obatoclax interaction with the BCL-2 family member protein MCL-1 was essential to the process, resulting in its disassociation from the BH3 domain protein Beclin-1. Initiation of authophagy followed and was dependent on the activity of a specific kinase, RIP, that in turn was tightly controlled by the cylindromatosis de-ubiquitinase. Collectively, these studies provide a new therapeutic avenue for treating corticosteroid-resistant ALL with obatoclax.

The importance of this paper to the fields of molecular pharmacology, autophagy, and the biology of pediatric ALL are numerous. Whereas the number of papers that have linked the BCL-2 family member protein MCL-1 to disrupting apoptosis are numerous, herein the authors show that this same protein also interacts with the BH3 domain protein Beclin-1, thereby preventing initiation of autophagy. Although obatoclax and dexamethasone have no direct interaction with mTOR, their combination in ALL cells inhibits this enzyme through uncertain mechanisms with similar down-stream effects including induction of autophagy. Finally, whereas autophagy in CML is actually a protective mechanism of death from therapeutics such as imatinib, the authors demonstrated that this process facilitates tumor death with relative selectivity with the therapeutic agent obatoclax. The compelling *in vitro* and *in vivo* data with steroid-resistant ALL cells provide strong justification of clinical trials combining corticosteroids with obatoclax in relapsed, resistant ALL. Given the poor outcome of such patients, it is hoped that this outstanding study will favorably affect survival of some patients with refractory ALL.

JOHN C. BYRD, MD
Dr. Byrd indicated no relevant conflicts of interest.

The Elusive Leukemia Stem Cell

Taussig DC, Vargaftig J, Miraki-Moud F, et al. Blood. 2010;115:1976-1984.

Cancer stem cells (CSCs), i.e., a subset of cancer cells that display an unlimited capacity to undergo self-renewal and to give rise to a more phenotypically diverse malignant cell population, are the subject of intense interest and, to a certain extent, controversy. While some argue against the significance or even existence of these cells, there is a general consensus that if such cells exist, leukemia stem cells (LSCs), or leukemia-initiating cells (LICs), represent their prototype. Accordingly, extensive efforts are currently underway to characterize LICs, with the ultimate goal of developing strategies to eliminate them.

The initial characterization of LICs as cells expressing CD34 and lacking CD38 was described by the pioneering work of John Dick and colleagues. They discovered that cells capable of initiating leukemia in immunodeficient SCID mice resided within the $CD34^+$, $CD38^-$ population and postulated that such cells represented true LICs. Recently, this concept was challenged when Bonnet and colleagues from London reported that antibodies directed against CD38 inhibited engraftment of LICs in SCID mice,[1] suggesting that, at least in some cases, LICs may reside in the $CD38^+$ population. In this new paper from Bonnet's group, they showed that in certain types of leukemia LICs may, contrary to all conventional wisdom, emanate from the $CD34^-$ cell fraction. Specifically, they reported that in *nucleophosmin (NPM)*-mutated AML, the cells capable of initiating leukemia in SCID mice resided exclusively in the $CD34^-$ fraction in half of the cases. In the remaining cases, considerable heterogeneity was observed; some exhibited a more primitive phenotype ($CD34^+$, $CD38^-$), whereas others displayed a more progenitor-like phenotype ($CD34^+$, $CD38^+$). One possible explanation for these novel findings lies in the fact that leukemia cells from patients with a poor prognosis are more likely to initiate leukemia in immunodeficient mice. Because *NPM*-mutated leukemia carries a generally favorable prognosis, less information about the characterization of LICs in this subtype has been available. In any case, these new findings make several important points: the phenotype of LICs may be considerably more heterogeneous than previously thought, and such disparate phenotypes can in fact co-exist within individual leukemia cell samples.

These new findings could have significant implications for attempts to eradicate LICs with targeted therapies, particularly those employing approaches directed against leukemia cell surface antigens. They could also prompt a reappraisal of the optimal use of molecularly targeted agents to eliminate LICs. Although it has not yet been definitively proven, the concept that residual LICs are responsible for or contribute to relapse in AML remains plausible and unquestionably needs to be tested. However, until and unless LICs can be clearly defined, such efforts may be doomed to fail. To test the leukemia stem cell hypothesis definitively, it may be necessary to define LICs in relation to the genetic background of the AML subtype in question, and possibly even in individual patients. Despite the questions raised by this report, the findings presented could ultimately lead to more rational (and hopefully more effective) approaches to leukemia therapy.

1. Taussig DC, Miraki-Moud F, Anjos-Afonso F, et al. Anti-CD38 antibody–mediated clearance of human repopulating cells masks the heterogeneity of leukemia-initiating cells. Blood. 2008;112:568-575.

STEVEN GRANT, MD

Dr. Grant indicated no relevant conflicts of interest.

Promoting the Pericyte: Modeling the Anti-Angiogenic Effects of Thalidomide in HHT

Lebrin F, Srun S, Raymond K, et al. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. Nat Med. 2010;16:420-428.

"Circumstances do not make the man, they reveal him." – James Allen

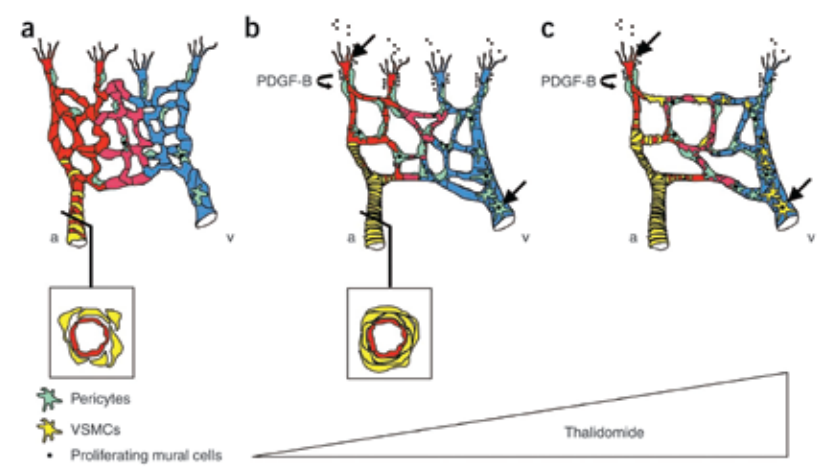
Characteristic congenital limb malformations (phocomelia) are synonymous with the medical tragedy wrought by thalidomide in pregnant women in the late 1950s and early 1960s. Unraveling the teratogenic basis of thalidomide morphed into a more general investigation of its modes of action which have been attributed to anti-angiogenic, immunomodulatory, and anti-inflammatory properties. A resurgence of interest in thalidomide for various non-hematologic and hematologic conditions ultimately led to its FDA approval for erythema nodosum leprosum and multiple myeloma (MM) and the approval of its derivative lenalidomide for MM and myelodysplastic syndrome with the del (5q) chromosome abnormality.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder primarily related to mutations in activin-like receptor kinase-1 (ALK1) and endoglin (ENG), which serve as receptors for the transforming growth factor-beta (TGF-β) family of ligands. In the normal state, endothelial cell-pericyte contact and vessel stabilization are maintained via a feedback loop involving TGF-β1 signaling through endoglin and Alk-1. In HHT, disruption of this signaling loop is felt to contribute to excessive angiogenesis and, in turn, phenotypic hallmarks of the disease: telangiectasias and arteriovenous malformations (AVMs). Severe epistaxis and gastrointestinal bleeding leading to anemia are common, and life-threatening internal bleeding from AVMs may result in substantial morbidity or death.

Lebrin and colleagues from the laboratories of Anne Eichmann in Paris and Christine Mummery in Leiden have exploited HHT as a disease model to "reveal" the "circumstances" by which thalidomide exerts its anti-angiogenic effects. First, they showed that thalidomide could reduce the frequency of epistaxis and increase hemoglobin levels in a small cohort of HHT patients. In an experimental model of HHT, which employed the neonatal retinas of mice heterozygous for a null mutation in *ENG*, a dose-dependent effect of thalidomide was observed; relatively lower doses normalized excessive vessel sprouting, while higher doses markedly reduced angiogenesis. Thalidomide also promoted retinal vessel maturation by stimulating recruitment of pericytes and vascular smooth muscle cells to the vascular plexus. Thalidomide up-regulation of endothelial cell-derived, platelet-derived growth factor beta (PDGFβ) was identified as a likely paracrine mechanism for recruitment of pericytes, which express the PDGFβ receptor (PDGFRβ). In support of this hypothesis, they showed that inhibition of PDGFRβ signaling with imatinib counteracted thalidomide's effects on angiogenesis and on pericyte coverage of blood vessel endothelial cells. Thalidomide also exhibited direct effects on mural cell proliferation and behavior (e.g., development of membrane protrusions and branching extensions) that were independent of PDGFβ. In comparison to untreated HHT patients, the nasal mucosal skin biopsy of an HHT patient treated with thalidomide (100 mg daily) revealed increased numbers of smooth muscle layers surrounding blood vessels, recapitulating findings from the ENG-deficient mice.

Figure

Schematic illustration of how thalidomide normalizes vascular malformations in HHT.



a) Reduced expression of endoglin or ALK-1 in endothelial cells reduces pericyte recruitment. Smooth muscle cell coverage of arteries is irregular, and vessels show endothelial hyperplasia and irregular capillary diameter. b) A low dose of thalidomide normalizes vessel coverage defects and excessive angiogenesis by stimulating mural cell recruitment. Mechanisms of thalidomide-induced vessel maturation include increased PDGF-B expression from the endothelial tip cells, which attracts co-migrating mural cells, and direct stimulation of mural cell proliferation. c) A high dose of thalidomide enhances the number of mural cells expressing α-SMA, indicating vessel maturity, and inhibits angiogenesis. Black arrows indicate that thalidomide targets both endothelial tip cells and mural cells directly to control vessel growth and maturation. a = artery; v = vein.

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This study highlights the ability of thalidomide to reduce epistaxis in patients with HHT by promoting blood vessel maturation. In this experimental model of HHT, thalidomide's modes of action reflect direct and indirect effects on pericyte recruitment and activation rather than a primary effect on vascular endothelial cells. While the conventional wisdom regarding thalidomide's anti-angiogenic mechanisms may now need to be broadened, it is not clear whether the drug's known ability to interfere with tumor growth is similarly related to enhancement of vessel maturation. Nonetheless, development of therapies targeting vessel stability may prove fruitful for patients with malignancies or for conditions related to vascular malformations, such as angiodysplasia and HHT. These mechanistic data also merit a careful appraisal of the utility of anti-angiogenic drugs in these disorders, since small-molecule multi-kinase inhibitors, which target PDGFRβ, may prove detrimental.

JASON GOTLIB, MD, MS

Dr. Gotlib indicated no relevant conflicts of interest.

That Was Then, This Is Now

Roach JC, Glusman G, Smit AF, et al. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. Science. 2010;328:636-639.

In the not-so-distant future, clinicians may order whole-genome sequencing of patient DNA the way we now order an MRI. In the run-up to the routine clinical use of whole-genome sequencing, investigators are taking advantage of this remarkable technical achievement to characterize the human genome and to solve challenging genetic and pathophysiological problems.[1,2] In a recent publication in *Science*, the power and beauty of whole-genome sequencing was illustrated by the ingenious studies of a collaborative group of scientists led by David Galas and Leroy Hood from the Institute for Systems Biology in Seattle and Lynn Jorde from the University of Utah. The problem to be solved by the study (to identify the genetic basis of a rare autosomal recessive disorder) was straightforward, but the experimental design was inspired and the studies were made possible by the generosity and selflessness of the involved family. Roach, Glusman, Smit, and Huff, who shared first authorship on the paper, and colleagues identified a pedigree that consisted of a mother, a father, and two siblings, both of whom were affected by two distinct autosomal recessive disorders, Miller syndrome (postaxial acrofacial dysostosis) and primary ciliary dyskinesia. Sequencing the genome of the parents allowed the investigators to delineate precisely sites of recombination, and the results illustrate the remarkable genetic diversity that exists between siblings (Figure). The sibling pair was found to be only ~20 percent genetically identical, and the investigators took advantage of this finding to narrow their search for the disease-causing mutations (Figure). Reasoning that rare phenotypes would likely be encoded by rare nucleotide sequence variants allowed the investigators to further narrow the search for the disease-causing mutations. Data analysis identified sequence variants that fit the model of either simple recessive (a gene mutated at the same position in both alleles) or compound heterozygous (mutation of the same gene at different nucleotide positions in each of the two alleles) in four candidate genes. By comparing core exome sequencing of two unrelated individuals with Miller syndrome, the disease-causing mutation for Miller syndrome in the sibling pair was confirmed to be the consequence of a compound heterozygous state affecting dihydroorotate dehydrogenase *(DHODH)*, a gene that encodes a key enzyme in pyrimidine biosynthesis. The gene (*DNAH5* that encodes a dynein protein that functions as a force-generating protein with ATPase activity) that is mutated in primary ciliary dyskinesia was previously known, and the studies by Roach et al. confirmed that the gene was mutated in a compound heterozygous state in the two affected siblings. As such, primary ciliary dyskinesia served as a positive control for the studies. In the process of discovering the genetic mutation that causes Miller syndrome and confirming the genetic basis of primary ciliary dyskinesia, Roach and colleagues reported a number of other interesting, basic observations including the following:

- Recombination in maternal meioses occurs ~1.7 times more frequently than in paternal meioses (98 maternal events compared to 57 paternal events).
- 92 of the 155 recombinations took place in a known genetic hotspot.
- There are ~70 mutations/diploid genome, resulting in a mutation rate of ~1.1 x 10^{-8} per position per haploid genome.
- The mutational frequency at CpG sites (sites of genomic methylation) is ~11 times greater than at other sites.
- 323,255 novel single nucleotide polymorphisms were identified.

Recalling the progress that has ensued since the National Center for Human Genome Research was established in 1990 with a goal of sequencing the human genome in 15 years, the studies of Roach and colleagues bring to mind a quote from Arthur C. Clarke: "Any sufficiently advanced technology is indistinguishable from magic."

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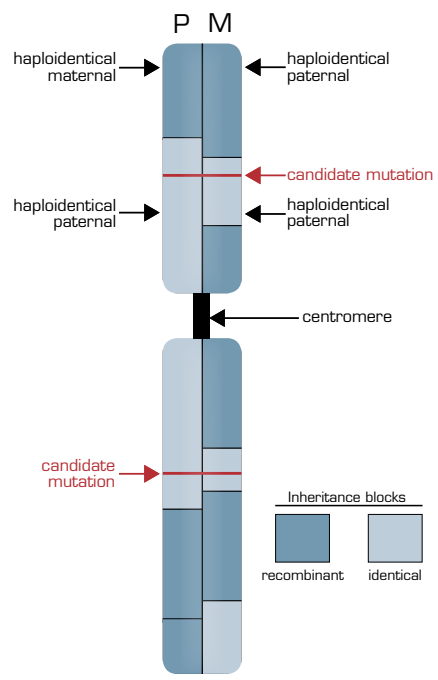
2. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009;361:1058-1066.

Figure



Deep sequencing of the pedigree reveals the extensive nature of genetic recombination

The illustrated chromosome is vertically split to depict the inheritance state from the father (P, left half) and the mother (M, right half) based on nucleotide sequencing of the genomes of the parents and the two children in the pedigree. Mendelian inheritance patterns can be grouped into four states for each polymorphic nucleotide position with children receiving one of the following: a) the same allele from both the father and the mother (identical); b) the same allele from the mother but the opposite allele from the father (haploidentical maternal); c) the same allele from the father but opposite from the mother (haploidentical paternal); and d) opposites from both parents (non-identical). In the illustration, the pattern of inheritance is shown in blocks, with the dark blocks representing regions of recombination that occurred in the parental germ line during meiosis. In areas where a light blue segment abuts a dark blue segment, the siblings are haploidentical (paternal or maternal). In areas where a dark blue segment abuts a dark blue segment, the siblings are non-identical. Only in those regions in which light blue portions of the schematic karyotype are adjacent are the siblings effectively twins. Overall, 22 percent of the siblings' genomes were found to be identical. This finding markedly narrowed the area that needed to be searched for the disease-causing mutations (red horizontal lines), as a recessive inheritance pattern was suggested to account for both Miller syndrome and primary ciliary dyskinesia.

CHARLES PARKER, MD

Dr. Parker indicated no relevant conflicts of interest.

New Iron Age

Callens C, Coulon S, Naudin J, et al. J Exp Med. 2010;207:731-750.

The iron age, which began in Asia and Greece before migrating to Europe in 8th century B.C., ushered in significant changes in society when cutting tools and weapons were made with iron or steel. Besides its importance in tools and weapons, iron is essential to life in nearly all organisms. In cells, iron exists in the ferrous (Fe2+) and ferric (Fe3+) states that participate in the generation of reactive oxygen species and is stored in metalloproteins, since free iron can lead to production of toxic free radicals. In our bodies, iron is incorporated into the heme complex, specifically in special carrier proteins such as hemoglobin or myoglobin, and it is also required as a cofactor for critical cellular enzymes involved in metabolism and proliferation.

Because of problems associated with free radical generation, iron is tightly regulated through transferrin, which binds to iron as it is absorbed in the duodenum. The transferrin receptor (TR) is evolutionarily conserved and is a validated target for cancer therapy. Targeting TR in cancer cells would lead to iron depletion and therefore cell death. Earlier studies have suggested that iron chelators could be used as cancer therapies. In this paper, Callens et al. from the laboratories of Ivan Moura and Olivier Hermine in Paris, suggest that iron homeostasis is a good target in AML. They begin with the demonstration that iron chelation inhibits proliferation and induces monocyte differentiation in HL60 cells, and that 30 percent of the genes most strongly induced by iron deprivation were also targets of vitamin D3, a known differentiation agent. They demonstrated that iron chelation induced expression and phosphorylation of the vitamin D3 receptor and that the combination of iron chelation and vitamin D3 acted in a synergistic fashion. They then demonstrated the same effect with fresh AML blasts and showed induction of differentiation of the cells by measuring an increase in CD11b and CD14 expression. Furthermore, they demonstrated a similar drive to differentiation into monocytes with CD34+ cord blood progenitors. Mechanistically, the differentiation was felt to be through modulation of reactive oxygen species expression and the activation of mitogen-activated protein kinases (MAPKs). Finally, they treated a single patient with recurrent AML with the iron chelator desferoxamine and the vitamin D metabolite hydroxycholecalciferol. The patient showed a partial reversion of pancytopenia accompanied by an increase in monocyte numbers. The normal-appearing monocytes, but not lymphocytes or NK cells from the treated patient, contained the same trisomy 8 present in the original blasts.

These data suggest that the availability of iron may be important, especially in diseases such as AML that have a very high turnover of cells. The sequential events of iron deprivation, MAPK activation, and amplification of vitamin D receptor expression and phosphorylation lead to monocyte differentiation in malignant and normal precursor cells. These schema alone or combined with other differentiation agents could prove to be an important advance in the treatment of patients with AML.

NELSON J. CHAO, MD, MBA

Dr. Chao indicated no relevant conflicts of interest.

Allogeneic Transplantation 2010: A Tale of Two Diseases

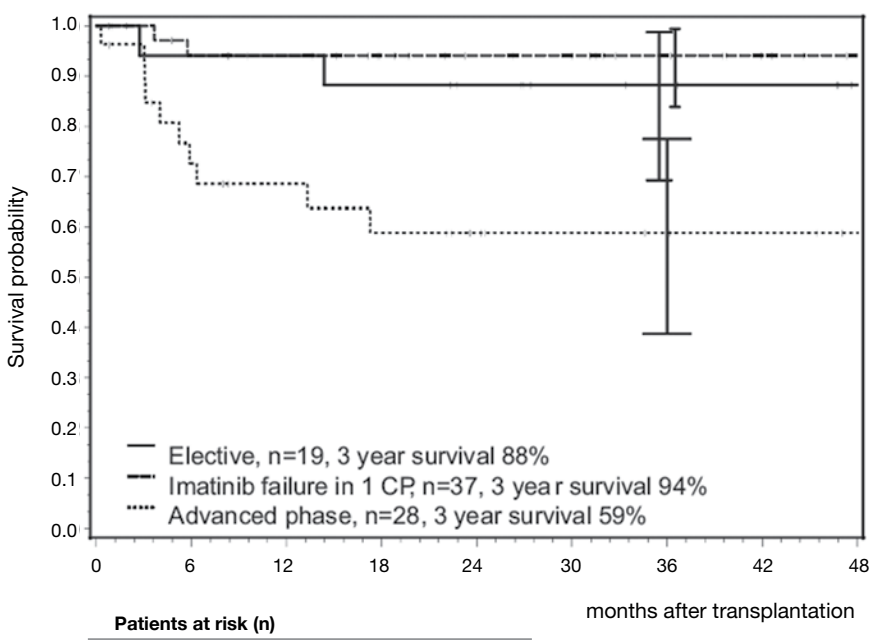
Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood. 2010;115:1880-1885.

Litzow MR, Tarima S, Pérez WS, et al. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia. Blood. 2010;115:1850-1857.

The use of allogeneic transplantation is largely shaped by the availability of less toxic but effective therapies. Thus, while "curative" in chronic myeloid leukemia (CML), upfront tranplant has been displaced by imatinib and now is only employed in cases of refractory or advanced-phase disease. However, for secondary myelodysplastic syndrome (MDS), attempts to use effective chemotherapy have been unsuccessful, and transplantation may offer the only hope. Two recent studies help us define the efficacy of transplant for these two diseases.

Imatinib is remarkably effective in chronic-phase CML; most patients who remain on the drug will obtain a complete cytogenetic remission and will have an excellent disease-free survival. However, some studies suggest that imatinib is less effective in the general community than in the controlled setting of clinical trials,[1] and in one large trial, 40 percent of patients stopped therapy,[2] most often for toxicity or lack of efficacy. Secondary therapy with next-generation tyrosine kinase inhibitors (TKIs) can salvage approximately half of those patients, leaving a moderately large niche for transplantation. The German CML Study IV recently reported their results on 84 patients who received a matched allogeneic transplant because of either a high-disease risk score at diagnosis, imatinib failure, or progressive disease. The three-year survival was excellent, at 91 percent for chronic-phase cases and 59 percent for advanced-phase patients (Figure 1). Moreover, nearly 90 percent of the survivors were in complete molecular remission. Regimen-related mortality was only 8 percent. A matched comparison of chronic-phase patients who received transplant compared to imatinib showed no difference in survival at the three-year mark. These impressive results suggest that in the modern era, with better conditioning regimens, patient selection, and supportive care, transplantation should be considered early in patients with a poor response to initial TKI therapy.

Figure 1



Patients at risk (n)

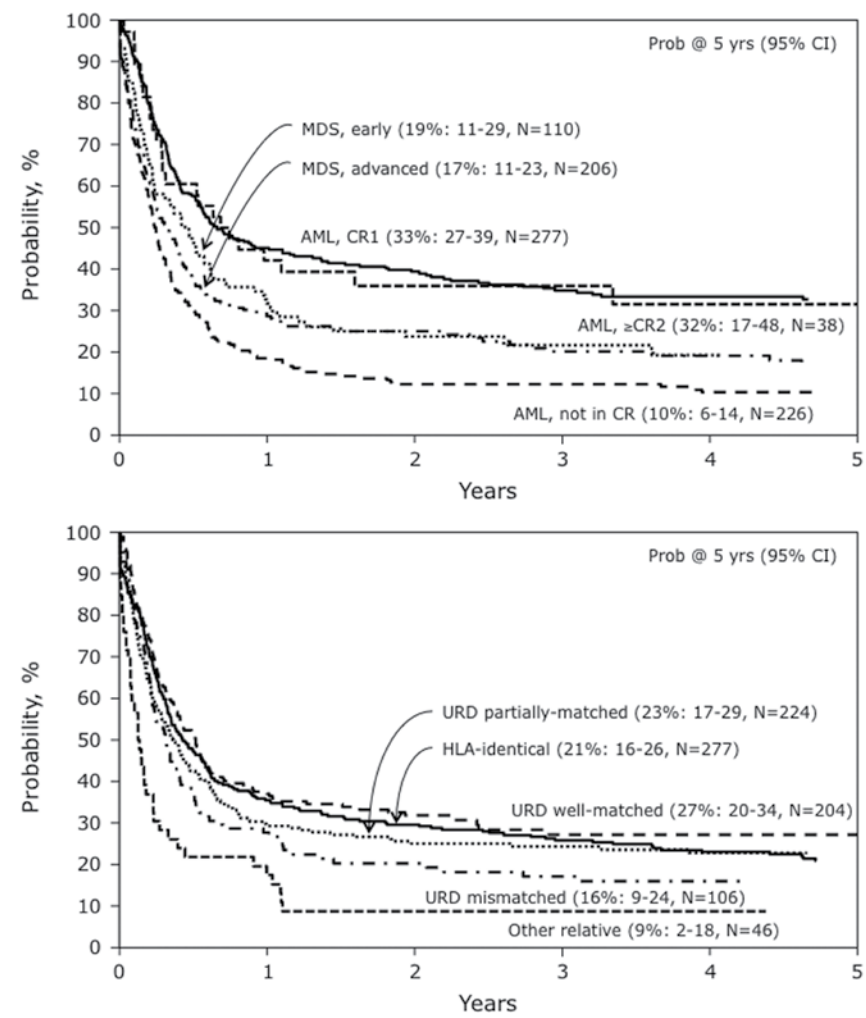
Month	0	12	24	36	48
Elective	19	16	13	9	5
Imatinib failure	37	27	17	10	3
Advanced phase	28	14	8	5	2

Probability of overall survival after allogeneic transplant is shown in the top figure. The box on the bottom shows a matched pair analysis comparing chronic-phase patients receiving transplantation compared to patients receiving imatinib therapy

This figure was originally published in *Blood*.

While the role of transplantation has properly diminished in CML, a different dynamic exists for secondary MDS, which is exceedingly resistant to chemotherapy approaches. A large study by the Center for International Bone Marrow Transplant Research examined the role of transplantation in treatment-related MDS (323 cases) and AML (545 cases). Perhaps owing to the heavy pretreatment of these patients compared to the CML experience cited above, the regimen-related mortality after one year was 41 percent and at five years was 48 percent. The relapse and overall survival rates at five years were 31 and 22 percent. The authors developed a risk model, using age (> 35 years), poor-risk cytogenetics, lack of remission, and the use of a poorly HLA-matched donor, and showed that survival mapped closely to the accumulated score. Patients with no points had a five-year survival of 50 percent while only 4 percent of those with the most points (four) survived five years (Figure 2). Thus, though the aggregate outlook of these patients following transplant is poor, certain subsets enjoy a reasonable chance at a potentially curative therapy.

Figure 2



Probability of overall survival after allogeneic transplant for t-MDS (top panel) and t-AML (bottom panel), based on risk score

This figure was originally published in *Blood*.

As clinicians, it is important to consider that the success of transplantation is largely an issue of appropriate timing. Finding a donor, be it related or unrelated, takes time, sometimes several months. Thus, planning is key. For CML, one should not wait for a patient to be resistant to all TKI therapy before starting a donor search, as these patients are more likely to progress to advanced-phase disease, where the efficacy of transplantation is greatly diminished. For therapy-related MDS and AML, HLA typing and donor search should be instituted as soon as possible. Moreover, alternative sources, such as umbilical cord stem cells, can be considered for patients for whom a donor is not available.

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2. Druker BJ, Guilhot F, O'Brien S, et al. Long-term benefits of imatinib (IM) for patients newly diagnosed with chronic myelogenous leukemia in chronic phase (CML-CP): the 5-year update from the IRIS study. J Clin Oncol. 2006 ASCO Annual Meeting Proceedings Part I. 2006;24:6506.

JERALD RADICH, MD

Dr. Radich indicated no relevant conflicts of interest.

Clinical Trials Corner

Beginning with this issue, a new feature called "Clinical Trials Corner" will appear in *The Hematologist* on a regular basis. This concept was developed by our Editorial Board in response to feedback from readers asking for information on important, ongoing clinical trials. Under the direction of Dr. Charles Parker, who will assume the role of Coordinating Editor for this section, the Contributing Editors will provide brief updates and summaries on a small selection of ground-breaking clinical trials taking place in our field. The goals of this column are to raise awareness of these trials and to provide insights into the research directions being pursued in the field in advance of specific knowledge of trial results. We look forward to receiving your comments and suggestions regarding this new feature.

Myeloproliferative Neoplasms

STUDY TITLE: Randomized Trial of Pegylated Interferon Alfa-2a Versus Hydroxyurea Therapy in the Treatment of High-Risk Polycythemia Vera and High-Risk Essential Thrombocythemia

SPONSORED BY: The Myeloproliferative Disorders Research Consortium

PARTICIPATING CENTERS: This is an international study that includes 40 medical centers in North America (19) and Europe (21).

STUDY DESIGN: Open label, randomized study comparing treatment with hydroxyurea with that of pegylated interferon alfa-2a in patients with high-risk polycythemia vera (PV) and high-risk essential thrombocythemia (ET). Patients will be treated for up to 12 months to achieve a complete response (CR) or a partial response (PR). Patients who achieve a CR or PR will be treated and followed for a maximum of four years.

- Patients with high-risk PV are defined as having one of the following characteristics: age > 60 years; previously documented thrombosis; erythromelalgia or migraine either after diagnosis or within 10 years before diagnosis and considered to be disease-related; significant splenomegaly (i.e., > 5 cm below costal margin on palpation) or symptomatic splenomegaly (pain, early satiety); platelets > 1,000 x 10^9/L; or diabetes or hypertension requiring pharmacological therapy.
- Patients with high-risk ET are defined as having one of the following characteristics: age > 60 years; platelet count > 1,500 x 10^9/L; previous thrombosis; previous hemorrhage related to ET; or diabetes or hypertension requiring pharmacological therapy.

SAMPLE SIZE: 306 patients with high-risk PV and 306 patients with high-risk ET.

RATIONALE: Although earlier investigations clearly demonstrated that interferon has activity in patients with PV and ET, more recent studies demonstrate that interferon could induce both hematologic remissions and cytogenetic responses based on quantitation of the mutant allele burden in patients with JAK2V617F-positive disease. In some JAK2V617F-positive patients, the abnormal allele was no longer detectable by sensitive PCR techniques, suggesting that the mutant clone can be eradicated by treatment with interferon. The pegylated interferon that will be used in this study may be better tolerated than previous formulations of the recombinant protein. While the primary objective is to compare the complete hematologic response rates for the two treatments, the study incorporates a number of interesting secondary objectives including the following:

- To compare the impact of therapy on several key biomarkers of the disease (JAK2V617F allele burden, hematopoietic cell clonality in platelets and granulocytes in female patients, bone marrow histopathology, and cytogenetic abnormalities)
- To estimate survival and incidence of development of myelodysplastic syndrome, myelofibrosis, or leukemic transformation after therapy
- To estimate the incidence of major cardiovascular events (defined as cardiovascular death, myocardial infarction, stroke, transient ischemic attack, pulmonary embolism, Budd–Chiari syndrome, deep-vein thrombosis, and any other clinically relevant thrombotic events)

COMMENT: This is a timely translational study that incorporates relevant clinical endpoints with basic studies suggested by recent developments in the understanding of the pathobiology of myeloproliferative neoplasms. Substantive new information will certainly accrue from this comprehensive, well-designed study. A companion study titled "Single Arm Salvage Therapy With Pegylated Interferon Alfa-2a for Patients With High-Risk Polycythemia Vera or High-Risk Essential Thrombocythemia who are Either Hydroxyurea Resistant or Intolerant or have had Abdominal Vein Thrombosis" will be launched simultaneously and will have the same organizational structure as that of the randomized study. The enrollment goals for the non-randomized study are as follows: 84 patients with high-risk PV, 84 patients with high-risk ET, and up to 20 patients with splanchnic-vein thrombosis.

– Charles Parker, MD

Hemophilia A

STUDY TITLE: Rituximab for the Treatment of Inhibitors in Congenital Hemophilia A (A TMH CTN Study)

COORDINATOR: Transfusion Medicine/Hemostasis Clinical Trials Network

SPONSOR: National Heart, Lung, and Blood Institute (NHLBI)

LOCATIONS OF TRIAL: 21 U.S. medical centers will enroll patients

ANTICIPATED ACCRUAL: 50 patients

RATIONALE AND SIGNIFICANCE: One-third of individuals with severe hemophilia A (< 1% of normal factor VIII [FVIII] activity) develop neutralizing anti-FVIII allo-antibodies. Bleeding patients with high-titer FVIII inhibitors require alternative or bypassing factors, such as recombinant factor VIIa and prothrombin complex concentrates. Immune tolerance induction protocols can suppress allo-antibody titers, but durable responses require frequent, prolonged, and expensive FVIII infusion schedules. Recent anecdotal observations suggest that rituximab can reduce anti-FVIII titers. This phase II, non-randomized, multicenter trial is designed to assess the benefits and safety of rituximab in individuals ≥ 18 months old with severe congenital hemophilia A and a past history of anti-FVIII inhibitor ≥ 5 Bethesda units (BU)/mL. Study participants who mount an allo-antibody recall response ≥ 5 BU/mL after FVIII infusion will receive four weekly rituximab doses. If the inhibitor titer falls below 5 BU/mL, another FVIII infusion will be given, and the allo-antibody levels will be further assessed. The primary study outcome is the proportion of patients with inhibitor levels < 5 BU/mL at weeks six through 22 post-rituximab and with < 5 BU/mL titer after FVIII rechallenge. Secondary outcomes include the proportions of patients with minor allo-antibody responses to rituximab and the frequency and severity of treatment-related adverse events.

COMMENT: While the scope is purposely limited by the phase II design, this pilot study should provide important preliminary data on the frequency and depth of anti-FVIII allo-antibody responses to rituximab along with an assessment of short-term safety. If the results are positive, a larger randomized clinical trial to compare this approach to immune tolerance induction will be justified. The ultimate goal is to identify the most beneficial, safe, and cost-effective strategy for those challenging patients with severe hemophilia A and high-titer inhibitors.

– Michael Linenberger, MD

Hodgkin Lymphoma

STUDY TITLE: RATHL: Phase III Randomized Study of Response-Adapted Therapy Using Fludeoxyglucose F18(FDG)-PET/CT Imaging in Patients With Newly Diagnosed Stage II-IV Hodgkin Lymphoma

COORDINATORS: The UK National Cancer Research Institute Lymphoma Clinical Studies Group through the Cancer Research UK/UCL Trials Office, London. In collaboration with the Gruppo Italiano per lo Studio dei Linfomi, the Australasian Leukaemia and Lymphoma Group, the All Ireland Cooperative Oncology Research Group, and Centres in the Nordic Countries.

STUDY DESIGN: Exactly 1,200 patients will be registered in the trial after full staging including FDG-PET imaging. All patients receive two courses of full-dose ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) chemotherapy and then undergo a repeat FDG-PET scan. Patients who become PET-negative are randomized between ABVD and AVD, the omission of bleomycin aiming to reduce lung toxicity while achieving an equivalent outcome. Those who remain PET-positive undergo treatment escalation with the BEACOPP (bleomycin, etoposide, doxorubicin [Adriamycin], cyclophosphamide, vincristine, procarbazine, prednisone) regimen, thereby attempting to improve remission rates.

RATIONALE: Advanced Hodgkin lymphoma is often curable, but with standard ABVD chemotherapy initial treatment still fails in around one-quarter of patients, and, in those who are cured, late toxicity remains a significant problem. Cure rates might be increased using more intensive initial treatment, but the resulting toxicity would be unacceptable if those with a good chance of cure using standard therapy were subjected to the high-dose regimen. Baseline clinicopathologic characteristics are poor discriminators in this respect, but there is increasing evidence that FDG-PET functional imaging can give accurate prognostic information if performed early during the course of treatment. The aim of this trial is to prospectively evaluate the use of FDG-PET in early assessment of treatment response. The imaging information will guide selective escalation of therapy for those with a poor prognosis and provide the basis for testing de-escalation of treatment to minimize long-term toxicity for those with a good initial response.

COMMENT: An important issue for PET scanning that has not been adequately addressed in publications to date is that of reproducibility. The interpretation of FDG-PET scans is an evolving field with person-to-person and center-to-center variation. This study uses a standardized approach to the central reporting of PET scan results, validated by using them to guide subsequent therapy. This trial is an important test of the prospective use of FDG-PET scanning to modulate the intensity of treatment for advanced Hodgkin lymphoma. The study will provide a high level of statistical power for the randomized question and will also give information on a large cohort of patients treated with intensification following a positive CT-PET scan. Because there will be some cross-over between the randomized arms, mainly with reduction of bleomycin dose for patients developing pulmonary toxicity, the power of the analysis may be slightly reduced.

– Peter Johnson, MD

Dr. Johnson is the principal investigator on this study.

Helen Margaret Ranney, MD (1920 – 2010)

On April 5, medicine lost one of its most distinguished physician-scientists with the death of Helen Ranney, a week short of her 90th birthday. In an era when we debate if any of us in medicine can still combine the famous triad of research, teaching, and patient care, she exemplified a quartet of skills that also included superb administrative abilities.

Further, Dr. Ranney developed and implemented these skills at a time when women were almost never accepted as major players in medicine — as she discovered in the rejection of her medical school application in 1941 when she graduated from Barnard College — but fortunately moving into an era of markedly increasing equity with regard to gender. As much as anyone, she was the role model for this equity by becoming the first woman to hold the title of chair of a department of medicine as well as the first woman president of both the American Society of Hematology and the Association of American Physicians.

In 2008, *The Hematologist* published a brief summary of Dr. Ranney's many accomplishments (*www.hematology.org/Publications/Hematologist/2008/1296.aspx*). We refer readers to this excellent article for its scientific information as well as vignettes and photographs. Below we add some further personal observations about her as a role model: for one of us in what is now called translational research and for the other as a clinician-teacher.

In her research role spanning almost 50 years, Dr. Ranney published slightly fewer than 100 papers. These studies range from sophisticated physical chemistry, to developing new techniques, to ground-breaking clinical observations. She pioneered the identification and routine clinical detection of new hemoglobin variants, the relevance of hemoglobin A1c to diabetes, and the study of intracellular protein interactions (in the red cell). Her research always went from the patient to the laboratory and back to the patient, not the "bench to bedside" model of today. When Dr. Ranney moved in 1960 from the Columbia University College of Physicians and Surgeons, where she had done all of her training, to Albert Einstein Medical College, she had the foresight to name her unit the "Heredity Clinic," foreshadowing the much later widespread development of medical genetics units.

As a clinician, Dr. Ranney kept abreast of the whole spectrum of hematology and even of internal medicine. Her skill in exploring the limits of knowledge of medical students, residents, and even hematology fellows at the patient's bedside, without embarrassments, was legendary. She delighted in the fact that the advances in hematology research had made it comparable in rigor to the physiological specialties, such as cardiology and nephrology, and that hematology could no longer be dismissed as "internal dermatology." However, she always remained cautious about the ever-changing contemporary enthusiasms of our profession for various claims of medical breakthroughs.

In 1973, the year that she was elected to the National Academy of Sciences, Dr. Ranney began her 13-year tenure as chair of the Department of Medicine at the relatively new University of California at San Diego (UCSD) School of Medicine. She is widely credited with molding this fledgling school into a strong academic institution and then holding it together despite the effects of another era of political turbulence in the state of California. The chair in medicine at UCSD is now designated as the Helen M. Ranney Distinguished Professor.

Dr. Ranney was the first woman to be named a Distinguished Physician of the Veterans Administration. After she stepped down from the position at UCSD, she remained active in the Veterans Administration Hospital. She also continued her work on the development of potential red blood cell substitutes for transfusion therapy. But in addition to these activities, she was always sought after as a consultant and remained uniquely savvy about topics such as the future of the National Institutes of Health Clinical Center, the development of separate hospitals for individual subspecialties, and many other issues that will affect academic medicine in the decades to come. There are very few individuals, in the past or now, who have had the impact that she did on our profession in general and hematology in particular.

Alan N. Schechter, MD, and Geraldine P. Schechter, MD

Update on Health Information Technology and Hematology: Electronic Health Record Certification

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ASH continues to monitor the status of electronic health record (EHR) development and implementation, including the Centers for Medicare and Medicaid Services (CMS) Electronic Health Record Incentive Program. ASH is encouraging CMS to assure widespread adoption of health information technology (HIT) by providing flexibility in the definition of meaningful use and in the timeframe for practices to adopt HIT, by limiting burdensome reporting requirements, and by harmonizing the incentive programs between Medicare and Medicaid. In this regard, recent developments regarding "certification" of EHRs are of significant interest. Hematologists engaged in purchasing decisions for EHRs should be aware of the importance of a certified product and changes that are underway in how the Department of Health and Human Services (HHS) certifies organizations such as Certification Commission for Health Information Technology (CCHIT).

On March 1, 2010, the CCHIT announced plans to extend comprehensive certification to hematology/oncology applications. This is a positive development because certification of EHR assures patients and physicians that the product meets basic functionalities including interoperability and security features. Certification programs approved by HHS will also be required for applications to be used in evolving federal programs to incentivize physicians in the meaningful use of EHRs.

On March 10, 2010, HHS issued a notice of proposed rulemaking requesting comments regarding the establishment of certification programs for purposes of testing and certifying health information technology. Details may be found on an HHS website, *http://healthit.hhs.gov*.

Based on comments received, two types of certification programs are now available from CCHIT: a temporary program to assure the availability of certified EHR technology prior to the date on which health-care providers seeking the incentive payments would begin to report demonstrable, meaningful use of certified EHR technology and a permanent program to replace the temporary certification program. According to the Certification Commission for Health Information Technology website, *www.cchit.org/get_certified*:

- "The CCHIT Certified® 2011 program includes a rigorous inspection of integrated EHR functionality, interoperability, and security according to criteria independently developed by CCHIT's broadly representative, expert work groups using CCHIT's published testing methods."
- "The Preliminary ARRA IFR Stage 1 program is simpler and more flexible, although it does not provide as much buyer assurance as the CCHIT Certified 2011 program. In this program, technology is only inspected to meet the certification criteria and standards in the HHS, Office of the National Coordinator Interim Final Rule of January 2010."

ASH Members' "Sage Advice" Shaped His Career

PAUL S. FRENETTE, MD

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Hematology is embedded in me. As an intern at McGill University, I vividly remember going to the office of Dr. Phil Gold, chair of medicine at the Montreal General Hospital, to ask for his permission to attend the American Society of Hematology's annual meeting in 1988 in Atlanta. Being from the French part of Canada, my English at the time was quite limited; I really had to muster up all my courage to enter the chairman's office for this unusual request. Dr. Gold, a wonderful physician-scientist who had become famous for his discovery of the carcinoembryonic antigen, enthusiastically supported the idea and became my first mentor and role model during my residency. I had such a wonderful time that I have returned to ASH nearly every year for the science, of course, but also to catch up with my friends.

Despite (or perhaps owing to) my limited experience in the lab, I was very interested in basic science research. At the time, hematology/oncology training programs in Canada were clinically oriented, and thus I came to the United States in 1991 to enroll in the Tufts New England Medical Center Program, which was headed by Dr. Bruce Furie. There, I had the privilege to learn clinical hematology with Drs. Jane Desforges and Bob Schwartz, giants of the field. In the fall of 1991, I attended a seminar by Dr. Denisa Wagner on the generation of P-selectin knockout mice. This was the hot new technology. Impressed by its potential power, I thought it would be very important to learn the technique. I joined Dr. Wagner's laboratory on a project to generate double-knockout mice lacking both P- and E-selectins in close collaboration with Dr. Richard Hynes at MIT. The project was extremely risky because the mice had to be generated from two rounds of homologous recombination of the cloned genomic DNA in embryonic stem cells, something that had never been done. If I had understood the difficulty and risks of the project, I probably would not have gotten involved. But I did, and, in the end, things worked out. Drs. Wagner and Hynes were a great collaborative team that basically brought me up as a scientist. As clinicians, we tend to be impatient and want to get results quickly. My first realization was that good research takes time, patience, and persistence.

Toward the end of my postdoctoral tenure, Dr. Barry Coller, who was the chairman of the Department of Medicine at Mount Sinai School of Medicine, came to Boston to give a seminar. After his seminar, he was interested in learning more about handling mouse platelets and our intravital microscopy studies. He asked me if he could watch me perform a tail vein injection in the basement of the old building where the Wagner lab was then located. Fortunately, despite my nervousness, I managed to properly inject into the mouse vein. This injection probably landed me my first faculty job.

Mount Sinai recruited me, through the Manhattan Sickle Cell Center headed by Dr. George Atweh, to evaluate the role of adhesion molecules in sickle cell disease using emerging mouse models. I knew nothing about red blood cells and thought it might be an interesting challenge. We used a genetically complex humanized mouse model that had been generated by Dr. Mohan Narla, who taught me a great deal about the disease, among other things.

... I was fortunate to become an ASH Scholar Award winner. This award was critical in providing my burgeoning research program the additional funding and freedom to test new, perhaps more risky, ideas.

Following my recruitment, Dr. Atweh's sage advice and mentoring were invaluable in these initial independent years to help me navigate through the difficulties of getting my first NIH grant. Although we had set out to investigate the adhesion mechanisms of sickle red blood cell (RBC) interactions with the endothelium *in vivo* in collaboration with Dr. Coller, we had observed that RBCs were mostly captured *in vivo* by leukocytes that were adherent in venules. This observation led us to investigate the role of the inflammatory response and pathological implications of these heterotypic interactions in thromboinflammatory diseases, a topic still active in my laboratory.

As a junior faculty member at Mount Sinai, I was fortunate to become an ASH Scholar Award winner. This award was critical in providing my burgeoning research program the additional funding and freedom to test new, perhaps more risky, ideas. During my last years as a research fellow at Harvard, I developed an interest in studying the mechanisms mediating hematopoietic stem cell trafficking between the bone marrow and blood compartments. Ultimately, this line of investigation has led us to make the unexpected observation that signals from the nervous system locally regulated the stem cell niche in the bone marrow. I am very proud that this work was selected for presentation at the ASH annual meeting Plenary Session each of the past two years. The dissection of the molecular and cellular constituents of the bone marrow niche represents another major area of ongoing research in the laboratory. I am extremely grateful for the dedicated students and postdoctoral fellows that have brought these projects and publications to fruition.

This July, I will be moving to Albert Einstein College of Medicine to become the first director of the Gottesman Institute of Stem Cell and Regenerative Medicine Research. I am excited to be given the opportunity to recruit several junior faculty members into the Institute. This will be a great way to expand my role as a mentor and give back to junior investigators.

WHAT'S ON THE WEB

The ASH website offers a **convenient way for ASH members to find information** relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH.

Featured in the Web spotlight this month is the Practice landing area of the ASH website, *www.hematology.org/practice*. **Clinicians are a key constituency of the Society,** representing a large percentage of our membership. As part of ASH's effort to keep hematology clinicians informed, numerous resources are provided through the Society's website.

Visit the "Practice" tab at *www.hematology.org* to:

- Get the latest clinical hematology news
- Access evidence-based guidelines and quick-reference tools on a variety of treatments and disorders
- Learn more about the Physician Quality Reporting Initiative (PQRI) and how you can participate
- View a list of opportunities to earn continuing medical education (CME) credits and lifelong learning points to maintain board certification
- Submit a clinical question through the Consult-a-Colleague program
- Read "Ask the Hematologist" articles from *The Hematologist*, a regular column that addresses specific treatment questions
- Download information about Medicare reimbursement
- Learn how to prepare in advance for an emergency to help minimize the impact on yourself, your patients, and your practice or institution
- Access a schedule of important dates and deadlines for meetings, award applications, and more
- Peruse the latest treatment articles in *Blood* and *The Hematologist* online

Read ***The Hematologist*** online at ***www.hematology.org/hematologist***, and catch up on the latest news in the field of hematology right at your desktop.

Mark Your Calendar

July

10 – 14 **World Federation of Hemophilia 2010 World Congress**
Buenos Aires, Argentina *www.wfh.org*

20 **Early-bird annual meeting registration open to ASH members**
Orlando, FL *www.hematology.org*

25 – 30 **Hemostasis Gordon Research Conference**
Waterville Valley, NH *www.grc.org*

August

1 **Deadline to submit active and international ASH membership applications**
Washington, DC *www.hematology.org*

4 **Annual meeting advance registration open to members and non-members**
Orlando, FL *www.hematology.org*

12 **ASH annual meeting abstract submission deadline**
Orlando, FL *www.hematology.org*

September

2 – 5 **First World Congress on Controversies in Hematology (COHEM)**
Rome, Italy *www.comtecmed.com/cohem/2010*

13 – 15 **2010 caBIG® Annual Meeting**
Washington, DC *https://cabig.nci.nih.gov/2010AnnualMeeting*

15 – 18 **Annual Meeting of International Society for Hematology and Stem Cells**
Melbourne, Australia *www.iseh.org*

22 – 23 **Beaumont's 19th Annual Symposium on Molecular Pathology**
Troy, Michigan *www.beaumont.edu/dnasymposium*

24 – 25 **2010 ASH State-of-the-Art Symposium**
Chicago, IL *www.hematology.org*

24 – 26 **Society for the Advancement of Blood Management 2010 Annual Meeting**
San Juan, Puerto Rico *www.sabm.org*

October

1 – 4 **Annual Meeting of the International Society for Biological Therapy of Cancer**
Washington, DC *www.isbtc.org*

10 – 13 **XXXIII World Congress of the International Society of Hematology**
Jerusalem, Israel *www.kenes.com/ish2010*

21 **Late-breaking abstract submission site opens**
Washington, DC *www.hematology.org*

21 – 24 **XI European Symposium on Platelet and Granulocyte Immunobiology**
Beaune, France *www.sfts.asso.fr*

21 – 24 **Congress of the International Society of Pediatric Oncology (SIOP)**
Boston, MA *www.siopboston2010.com*

22 – 24 **Annual European Hemophilia Consortium Conference**
Lisbon, Portugal *www.ehc2010.eu*